Study Protocol and Statistical Analysis Plan

PINPOINT: GAMING TECHNOLOGY TO ENGAGE ADOLESCENT SICKLE CELL PATIENTS IN PRECISION PAIN PHASE II

(5R44MD010746)

NCT04579926

09/17/2018

Study Protocol

2. SPECIFIC AIMS

Sickle cell disease (SCD) is the most common inherited blood disorder in the U.S.,[1] and affects 70,000 to 100,000 individuals primarily African Americans and Hispanics.[2-4] SCD is characterized by red blood cells (RBCs) which contain an abnormal type of hemoglobin, hemoglobin S (HbS). This abnormality causes RBCs to become sickle-shaped which results in the RBCs having difficulty passing through small blood vessels. This blockage reduces blood flow (i.e., vaso-occlusion) to tissues and vital organs[3,5,6] causing serious and life-threatening comorbidities such as organ failure, acute chest syndrome, and stroke.[7,8] Pain is the hallmark symptom.[9] Acute painful crises are the most common cause of healthcare utilization for people with SCD, and pain severity and frequency vary widely by individual.[10] SCD painful crises can last anywhere from a couple of hours to a couple of weeks and should be treated according to the severity of pain that is being experienced.[5]

Research suggests that painful episodes have phases, and can be categorized into different or specific types of pain.[11-13] Treating a crisis in the early stages can avoid peak pain when it is more difficult to treat,[14,15] and reduce the onset of irreversible tissue damage.[11] Thus, pain assessment methods which can recognize pain early as well as the type of pain experienced could potentially improve treatment outcomes. In previous studies, pain assessment has included self-reported diaries[16,17] and a variety of pain-scoring questionnaires[18-22], and more recently a mobile application ("app") to record and assess SCD-related symptoms in adults.[23] However, there remains a lack of valid and systematic methods of pain assessment for children resulting in a significant barrier to effective treatment of SCD pain.[24] Data suggests that children can be accurate self-reporters of pain as long as the measures are designed for children's developmental stage and cognitive abilities and can be rapidly completed with high engagement.[4] Therefore, novel approaches that are age-appropriate, and are easy and appealing to children may result in reduced barriers to pain assessment and better overall health outcomes.

Children are "growing up digital". Eighty-four (84%) of adolescents, ages 12-17, own a smartphone.[25] Over half of teens (58%) have access to a tablet device.[26] Data show that interactive technology can enhance children's learning and cognitive and social abilities,[27] and have sustainable effects.[28-30] "Gamification" is the use of game thinking and mechanics in non-game contexts.[31-33] Gamified applications use core game aspects such as fun, play, transparency, design and challenge, and apply them to real-world objectives.[34] Few products have been created applying gamification to clinical healthcare despite experts' suggestions that it would be highly innovative and effective.[35]

In our Phase I SBIR project, *Pinpoint: Gaming Technology to Engage Adolescent Sickle Cell Patients in Precision Pain Management,* we created and usability tested a prototype pain identification tablet app for teens with SCD. We created the Pain Assessment Tool (PAT) which consisted of transforming the pediatric Patient Reported Outcomes Measurement Information System (PROMIS) measures from a conventional paper format into a media-rich, interactive game response format. In addition, interactive modules focused on identifying, understanding, and communicating pain symptoms were initially prototyped. The technology applied in the Phase I study was specifically selected for fit with the target audience (i.e., teens); app-based and use of gamification approaches. The additional technological innovation proposed for the Phase II *Pinpoint* project is also well-suited to the targeted market (i.e., tablet and smartphone mobile-responsiveness). We have demonstrated the technical merit, feasibility, and market potential of the *Pinpoint* app in our Phase I project. The purpose of this Phase II application is to (1) continue research and development of the *Pinpoint* program with an emphasis on developing a scalable product for commercialization and (2) testing improvement in communicating about pain by the target users (teens with SCD). Specifically, this project will develop an app for use on smartphones and tablets for 13-17 year olds with SCD that will describe, categorize, and report pain experienced by adolescents with SCD, educate teens with SCD on effective strategies for communicating their pain to their adult care team (e.g., parents, family members, care providers), and educate teens on SCD disease care management. All aspects of the app will incorporate gaming principles which will engage adolescents and improve pain specification. The following **Specific Aims** will be achieved:

AIM 1: Develop a fully programmed, interactive *Pinpoint* app consisting of 5 modules addressing pain identification and communication.

AIM 2: Conduct usability testing of the *Pinpoint* app to evaluate the user interface, ease of use, and perceived barriers in order to optimize the app prior to large scale evaluation (n=14).

AIM 3: Test the full *Pinpoint* app with 13-17 year olds with SCD (n=100) using a within-subjects design to evaluate changes in (1) knowledge acquisition for communicating about pain and types of SCD pain; (2) the Pain Assessment Tool (gamified adaptation of the PROMIS measures)[36]; (3) SCD general knowledge and self-efficacy; (4) family cohesion; and (5) app usage.

Significance and innovation are high. *Pinpoint* will be the first app to identify and translate specific pain types for SCD into a gamified app using applied gamification principles while also instructing teens on how to effectively communicate their pain to others. *Pinpoint* also has strong clinical significance. It has the potential to be utilized in tandem with any pediatric care setting and can potentially reduce barriers to obtaining children's self-report by using a medium that they are comfortable with and enjoy, while providing important pain information that affect treatment choices and overall health.

3. RESEARCH STRATEGY

3A. Significance

3A.1. *Sickle cell disease is a prevalent disorder with significance public health impact.* Sickle cell disease (SCD) is a genetic disorder that affects red blood cells (RBCs), and is characterized by hemolysis,[7] vaso-occlusion,[7,8] and inflammation.[9] It is the most common genetic disorder in the U.S.[3] occurring in approximately 1 out of 365 African Americans and 1 out of 16,300 Hispanic Americans.[37] In SCD, hemoglobin molecules become dehydrated, deoxygenated, and "sticky" causing the molecules to clump and form long fibers.[3,5,6] This results in the RBCs changing into a crescent ("sickle") shape making the cells less flexible.[2,6] When the sickled cells block the flow of blood (vaso-occlusion[8]), a person with SCD may experience painful episodes (vaso-occlusive painful episode [VOEs]), and can experience permanent damage to tissue and vital organs,[3,5,6] acute chest syndrome,[5,36] and stroke.[1,2,5,6,8,9,38] SCD complications can be serious and have a significant impact upon well-being and quality of life.[5]

3A.2. *Sickle cell disease pain is the hallmark symptom of SCD, yet approaches to assess specific pain types are lacking.* SCD pain is multifactorial,[16,38] and can be triggered by identifiable (e.g., fatigue/overexertion,[9,14] cold temperatures,[14] dehydration,[14] emotional stress[39]) or unidentifiable factors.[8,11,40] In children with SCD, VOEs are the most common clinical problem[5] and the leading cause of hospital admissions.[3,8,11,39-41] Children are more likely to have longer hospital stays[41,42] and report significantly more severe pain.[42 41]VOEs become more frequent as children age,[18,43-45] and if left untreated, can result in morbidity and mortality.[46] The literature supports the concept that VOEs have different phases (e.g., pre-pain, pain start, pain acceleration, pain decline, etc.).[12,14,15,44,47] In addition, there are also three types of SCD pain: (1) acute recurrent painful crises; (2) chronic pain syndromes (i.e., pain lasting 3+ months); and (3) neuropathic pain.[11] The National Heart, Lung and Blood Institute (NHLBI) also identifies three types of SCD pain; acute, chronic, and mixed.[13] Effective SCD pain management requires both rapid and comprehensive assessments.[13,39] Rapid assessment focuses on the isolated pain event, pain intensity, and relief. Comprehensive assessment is used for chronic pain or as a follow-up to an acute pain episode and yields a multidimensional treatment plan involving the patient, family, and the healthcare team.[13 41]Research suggests that a simple measure which takes into account the child's developmental stage and cognitive abilities should be used when assessing pain.[4] Previous studies have assessed pain using self-reported diaries[16,1748,49]and validated measures.[18-22,18-2241,50]

Barriers to effective care for SCD pain in children include: clinicians who are concerned about the validity of a child's pain score; fear of negative effects from analgesic use; mistaking pain relief-seeking behaviors for drug-seeking behaviors[51]; and conflicting perceptions between patients, families, and medical professionals.[4] A lack of valid, consistent and systematic methods for child pain assessment is also a barrier.[24,46]While the validity of child pain self-report is a commonly reported barrier, most studies involving children and adolescents have shown that they are able to sufficiently report and describe their pain.[4,52,53]

3A.3. *Effective communication can improve psychosocial and health outcomes, yet child-centered communication training is remarkably uncommon.* There are a number of sequelae such as negative self-esteem, mood and anxiety disturbances, academic and peer relationship difficulties, and worry about the future which can impact a child with SCD.[22,54-56] Research suggests that cognitive-behavioral interventions can improve psychosocial and behavioral outcomes including communication skill building, yet the majority of interventions are parent-centered and do not focus on communication and social skills development with the child.[57,58] Children are capable communicators; by age 8, children can conceptualize complex health terms if asked in a format that boosts comprehension.[59-61] However children are typically relegated to the role of being the *receiver* rather than the *expressor* (i.e., sender) of information. A child's participation in health decisions can increase internal locus of control, decision-making ability, and adherence while lack of involvement can have adverse consequences (e.g., increased fear and anxiety, poor self-esteem, etc.[62-64]). Evidence suggests that regardless of age, the child's own perspective should be directly solicited and be given equal attention and merit as the parent's report, and that it is important for a child to participate in their health communication.[65-67] Thus, creating educational and skill-building interventions that use age-specific formats and designs (e.g., gamification) while reducing resource barriers (e.g., technology use) could improve skill acquisition for effective communication between SCD youths, their parents, and medical team.

3A.4. ***Children are high consumers of technology, but innovative approaches for assessing SCD pain are lacking.*** Children prefer using technology to learn and "gaming" is a popular approach. [28,68-70] Among 12-17 year olds, 97% (99% of boys, 94% of girls) play computer, web, portable, or console games.[71] The gaming industry is growing, and its principles are being applied to education and health. "Gamification" is a concept that translates games into a mechanism to promote desired behaviors; using game design in non-game contexts.[31,33,72-74] Despite its popularity, gamified approaches to assess child health are lacking especially for pain assessment. A literature review revealed only seven studies that have examined mHealth-based pain management approaches for adolescents with chronic pain.[17,75-79] One pilot study examined change in pain with the use of an app and found that pain-related outcomes appeared to improve; still, the remaining studies do suggest mHealth tools for assessing pain are feasible[76,80,81] and can yield high compliance.[75,80] Notably, only one study utilized a SCD population[80] and none included medical professionals within the context of program delivery. While there is lack of existent literature for mHealth and gaming formats for pain management among adolescents, interactive games can be especially effective in delivering health-related messages to youth.[82] The interactive games for health literature among youths has shown video games can improve self-efficacy; stimulate health discussions with friends, family and clinical team; encourage seeking support and advice; and can emphasize behavior acquisition via experiential learning rather than focusing on the learning of facts.[82] Interactive games can provide information about causes, treatments, and self-care options,[82] and can improve self-care and reduced emergency clinical utilization.[82]

3A.5. ***Use of well-established theories elevates significance.*** User-centered Design (UCD)[83,84]; Self-Determination Theory (SDT)[85,86]; and Social Cognitive Theory (SCT)[87] will be used. UCD solicits user input through iterative cycles, with adjustments made based on feedback,[88] resulting in greater user experiences and more reliable and effective results.[31,89] UCD will be used for the development of the *Pinpoint* games and preferred user-interface (UI). SDT involves factors that either facilitate or impede motivation and is a commonly used approach in health promotion.[90-94] In SCT, behavior is determined by environmental (social support, modeling) and cognitive factors (self-efficacy, self-concept). SCT has shown effectiveness in assessing and increasing health, as well as using virtual models.[95-99]

3B. Innovation

Pinpoint is a highly innovative project using gamification to create an adolescent SCD pain assessment tool based on the Patient Reported Outcomes Measurement Information System (PROMIS) measures.[36] *Pinpoint* will use theoretically-driven approaches, content from a best-selling book for teens with SCD,[100] and expert opinion and apply them to emerging technology to produce an industry-leading, innovative app that can impact the standards for SCD pain assessment and disease education. *Pinpoint* will be the first app to develop an assessment of specific SCD pain types into a gaming format and instruct children on how to effectively communicate about their pain to their adult care team (e.g., parents, teachers, healthcare professionals). It will also be the first translation of the pediatric PROMIS measures into a gaming format. Gamification for healthcare is an underutilized approach with high market potential. Games have been employed successfully for learning and with health promotion, yet gamified assessments and educational tools remain relatively undeveloped. *Pinpoint* applies “gaming” to pain assessment and disease education. Another innovation will be the potential clinical relevance of *Pinpoint*. Child pain assessment is complex and challenging, and there is data to indicate that VOE pain is often undertreated. [101] Research suggests discrepancies between SCD patient behavior and pain score which can lead to misunderstanding between providers and patients.[102-104] Pain severity is often verbally reported, yet evidence suggests that the majority of health professionals (up to 85% of doctors and 60% of nurses) believe verbal report is not a reliable indicator of pain intensity and inadequate pain assessment tools are one of the greatest barriers to SCD care.[102-104] This suggests that doctors are interested and may find clinical utility for a SCD pain tool that can be used by patients in their daily lives. Use of a SCD pain tool that bridges the gap between daily disease management and ongoing clinical care is likely to be utilized if it is (a) easy to use and interpret by all target audiences (patient, parent, provider); and (b) increases patient knowledge.[105,106] Patients require a tool that is easy-to-use and relatable; while medical staff require measures that are low burden, easily integrated into their practice, and facilitate care. The primary focus of *Pinpoint* in Phase II will be to educate the patient on how to better understand and communicate their pain to others, not create an app to be integrated into existing Electronic Health Records (EHR). Yet, the app will address many of the barriers of clinical uptake, because it can be easily incorporated into healthcare practice. Specifically, (1) gamification can increase engagement and autonomy of the patient to be more proactive in their care. *Pinpoint* will be built “by kids and for kids” serving as formative research for further integrating user-centered health assessments into clinical practice; and (2) the app will provide a feature that allows feedback from the patient to the provider to improve patient/provider communication.

3B.1. Market Potential. *Pinpoint* will have strong market potential because it (a) reaches an untouched and underserved population (SCD teens) with a program that will not only match their technology preferences but also provide them with critical health information using an interactive educational technology design; (b) has strong market potential with over 250 SCD centers in the U.S. who could purchase and provide the app to patients[107]; (c) can improve patient quality of care and information sharing; (d) is being developed with the leading SCD book publisher; and (e) will be a resource to physicians who act as proactive pain managers for patients. A multi-pronged marketing strategy is being proposed (see **Commercialization Plan**).

3C. Approach

3C.1. Phase I Overview and Outcomes. The Phase I project examined the feasibility and acceptability of a gamified tablet application (*Pinpoint*) intended to encourage teens (aged 13-17) to talk about and assess their SCD pain. The prototype was programmed for use on iOS and Android tablets. The Phase I project had three main goals: (1) consult with SCD experts to establish the core components of an app that could be used with children, parents, and providers to establish better pain identification and communication; (2) develop a functional prototype app with target audience input and feedback; and (3) assess the feasibility and acceptability of the app to guide future Phase II development. Phase I used multi-method formative research to guide app design and content prior to conducting lab usability testing of the app prototype to determine if it would be (1) feasible and (2) a product that teens with SCD would use. Phase I had 8 specific aims: (1) work with an Expert Advisory Board (EAB) of SCD experts to develop a new pain assessment tool (PAT) to engage adolescent SCD patients, improve pain specification by patients, and improve pain management by clinicians; (2) conduct cognitive interviews with 13-17 year old SCD patients to guide and refine the PAT and app concepts; (3) conduct focus groups with 13-17 year old SCD patients to guide and refine development of app content, design, and aesthetics to fully develop a functioning prototype; (4) program the PAT and UI elements into a tablet app prototype; (5) conduct usability testing with 13-17 year old SCD patients to assess functionality, navigation, and satisfaction; (6) conduct cognitive interviews with medical providers to provide input on app content, perceived barriers to use, and its potential for clinical use and integration to inform future implementation; (7) author a comprehensive Specifications Document to guide content development, UI design, and programming of the full-scale *Pinpoint* app in a future Phase II project; and (8) analyze data from cognitive interviews, focus groups, and usability testing sessions for the EAB to use along with the Specification Document to determine the feasibility of producing and evaluating a full-scale *Pinpoint* app in a future Phase II project. Deliverables were met and feasibility was confirmed by the EAB after a review of the Phase I findings. Phase I outcomes provided the necessary framework and data to guide Phase II goals: full-scale development of the app and testing the app in an experimental trial in Phase II.

Executive Summary of Phase I Findings: The prototype consisted of a gamified Pain Assessment Tool (PAT), gamified vocabulary game, interactive body scanner reflection activity, interactive educational self-disclosure activity, and excerpts from the *Hope and Destiny Jr.* book. Teens participated in cognitive interviews, focus groups, and usability testing (N=23). Of these participants, the average age was 14.7 ± 1.2 years, 43.48% were female, and 75% were diagnosed with Hb SS (n=23). The System Usability Scale (SUS),[108] a validated tool for assessing the usability and acceptability of technological products, served as the primary outcome. The SUS score (n=12) was 86.6 (68% is "above average"), suggesting a very high level of acceptability and usability among users. Healthcare providers were interviewed on the app's acceptability and potential function within the clinical practice (n=5). Providers gave the *Pinpoint* favorable scores with all responses yielding above average scores on a five-point Likert scale.

3C.1a. Phase I Aim 1. Gather input and evaluative feedback from an Expert Advisory Board (EAB). The EAB included experts in SCD, psychometrics, and gamification principles: (1) Deepika Darbari, MD, Children's National Medical Center in Washington, DC (CNMC-DC); (2) Allan Platt, PA-C, MMSc, author of *Hope and Destiny* and former Program Coordinator at the Georgia Comprehensive Sickle Cell Center at Grady Health System; (3) Lewis Li-Yen Hsu, MD, PhD, author of *Hope and Destiny, Jr.* and Professor and Director of Pediatric Sickle Cell at the Children's Hospital at the University of Illinois; (4) Julie Panepinto, MD, MSPH, Professor and Director of the Center for Clinical Effectiveness Research for the Children's Research Institute, Medical College of Wisconsin. She is a psychometrics expert, and has developed and translated several measures among SCD youth; (5) Talal Ziad Ali, PhD, MSN, RN (Wayne University) has studied the use of video games as a tool for decreasing pain in adolescents with SCD; and (6) Lauren Patrick, M.S., President of NetHealth, an expert in game theory application to healthcare.

Dr. Hilton Hudson (Co-I, and President of Hilton Publishing Company) facilitated the EAB which met formally four times. During the initial meetings, the EAB vetted the merit of establishing a new assessment tool versus using existing validated pain measures. The EAB unanimously agreed to use the PROMIS measures (see **3C.7.2.**) due to the clinical utility of the measures and that the pediatric PROMIS measures were currently being used in two clinical studies with pediatric SCD patients. The EAB agreed that additional pain identification and qualifiers were still needed since the PROMIS measures did not have targeted specificity for SCD pain. Thus, an interactive vocabulary game was brainstormed as an app activity. The objective of this activity was to have the user recognize and define vocabulary related to pain and its descriptors which could then be used to better categorize and specify pain type. Using a modified Delphi technique with 3 rounds and a card sorting series to finalize the grouping of the words, the EAB established a list of adjectives that were included in a word bank within the app that would allow app users to best describe the pain they are experiencing within particular areas of their bodies. Using the modified Delphi method, the EAB narrowed down the list from 137 words to a final word bank of 115 which were programmed as content in the interactive vocabulary game. The EAB also rank ordered *Hope and Destiny, Jr.* book content (see **3C.4.3a**) based on Phase I learning objectives. Twenty-two educational topics were identified, and 3 were programmed. The EAB provided valuable feedback in the formative stages of the app's development and concluded that Phase I results supported developing an enhanced version of the app and evaluating it for effectiveness in Phase II research.

3C.1b. Phase I Aim 2. Cognitive Interviews with Teens (Appendix A). Formative research approaches suggest that a low number of participants can be sufficient to guide formative development (i.e., 4-8 participants) if data saturation is present.[109] Our cognitive interviews (n=4) revealed a high level of agreement and thematic saturation was met. Teens were asked about their pain and previous assessments used, their communication strategies for discussing pain, use of apps and games for learning about SCD including preferred components and tracking features, and educational content that would be beneficial. Interviews revealed that teens experienced pain on average 2.5 times/week; an average of 1.5 times being "very bad". All teens reported telling their parents about pain and thought it was extremely important to discuss pain with their provider (avg.

score 9.25 out of 10). Desired app features were: (1) accurate pain scale; (2) information on new therapies and mediations; (3) how to stay healthy; and (4) general SCD information. Desired SCD-specific topics for educational content were: (1) how to stay healthy; (2) SCD studies and progress on cure; (3) gender-specific coping strategies; and (4) information on the different types of SCD.

3C.1c. Phase I Aim 3. Focus Groups (Appendix B). Two focus groups of 13-17 year olds with SCD informed prototype development. Focus groups ascertained whether the *Pinpoint* concept was easily understood and interesting, and identified whether the initially programmed features would be essential for a successful prototype. Focus groups were conducted in Charlotte, North Carolina as to broaden the geographical catchment of potential app users (per suggestion of the EAB). A total of 7 teens participated (3 females; 4 males). Formative data approaches suggest that 5-8 participants is sufficient to guide technology development,[109] and FG studies among SCD teens have successfully used comparable sample sizes.[110] Feedback influenced app modifications that were programmed into Prototype 2 and evaluated in lab usability. The focus groups evaluated the app's design, content and features, and overall engagement. Five activities (see **3C.1d**) were reviewed by the teens: (1) the Pain Assessment Tool; (2) the Self-Disclosure Activity; (3) Vocabulary Game; (4) Body Scanner; and (5) Pain Drawing Tool. The prototype was very well received; they thought it was understandable, logical, and easy to use. Participants reported high likeability for the gaming aspects including the sounds and visual effects, interactivity, and clarity of what was expected of the user. They found the content educational, useful, and fun. Average rating of the app was 7.8 out of 10. Input on what to modify or include for a fully programmed app included: optional narration, reducing the number of assessment questions, the option to show healthcare providers some of their responses but not all (non-pain items), daily push notifications to use the app, be able to send pain records to healthcare provider, include an eating and drinking log, blog and/or group chat feature, and interactive avatar character to guide the user through the app.

FIGURE 1: Homescreen

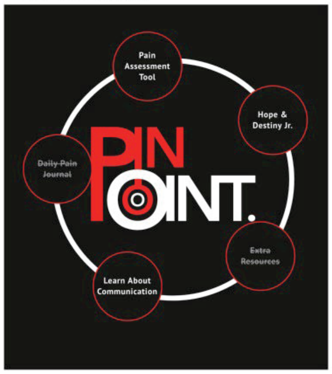
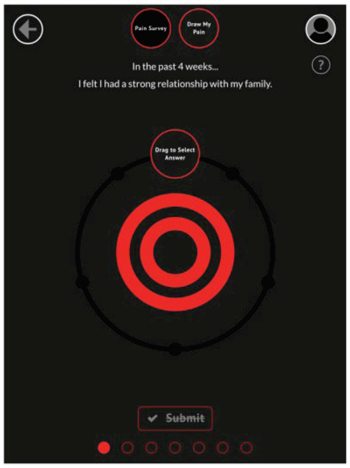


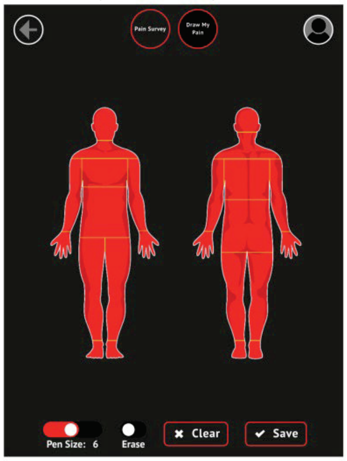
FIGURE 2: Pain Assessment Screen



In the past 4 weeks...
I felt I had a strong relationship with my family.

3C.1d. Phase I Aim 4. App Programming and Components. The prototype was built on a full stack web application using HTML/JavaScript as its main interface. AngularJS v1.6.3 was used as the front-end framework. Animations were performed using GreenSock Animation Platform and CSS 3 transitions. Look and feel was designed with Adobe Illustrator and developed using SASS and CSS 3.0 with HTML elements plus SVG, PNG, and JPG images and graphics. PHP was utilized to create spreadsheets populated with data collected from the front end. The application is hosted on a remote server provided by KB with the following infrastructure profile: Internet information must travel through KB's Sonicwall TZ600 firewall. Traffic then move to KB's web server, a Dell Power Edge T-430 with 128 GB of RAM, 4.5 TB available disk space on a RAID 5 redundant drive system using Windows HyperV Operating System. The virtual web server uses Windows 2012 IIS Web server software. Servers are kept in a locked room on site.

FIGURE 3: Body Scanner Activity

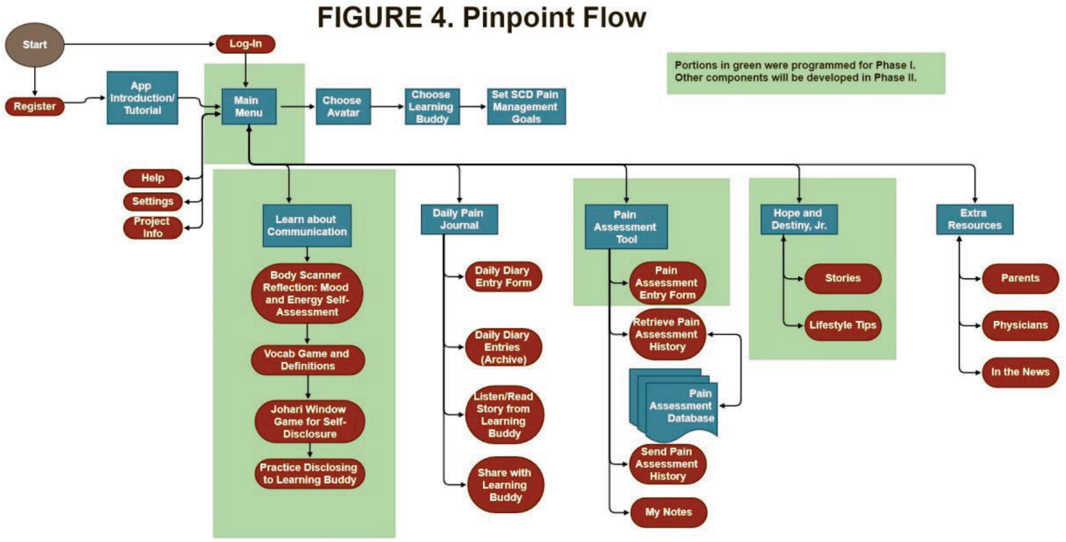


There are 3 app modules with 8 activities in the Phase I prototype: (Module 1) **Learn About Communication** which includes (a) Body Scanner Reflection activity, (b) Self-Disclosure activity, and (c) Vocabulary Game; (Module 2) **Pain Assessment Tool** which includes (a) interactive Pain Survey and (b) Draw My Pain activity; and (Module 3) ***Hope and Destiny Jr.* content** which includes (a) Lifestyle Tips, (b) "Stories", and (c) Glossary. The Body Scanner Reflection is a guided meditation that segments the body into 6 sections and encourages reflection of how the user's body feels. The Vocabulary Game has users match as many SCD pain related words with their definitions in a 2-minute timed game. The Self-Disclosure Activity teaches the different types of communication levels using a Johari window and allows users to test their knowledge with example characters. The Pain Assessment Tool is an interactive survey containing 56 questions about user pain. The Pain Drawing Tool requires users to draw their pain on a full body diagram. Lifestyle Tips provide educational content to help prevent pain episodes. The "Stories" provide motivational excerpts from teens with SCD, and the Glossary is a list of medical terms and definitions.

3C.1e. Phase I Aim 5. Lab Usability Test (Appendix C). Remote usability testing was conducted with 12 users recruited from Sickle Cell Disease Association of America (SCDAA) chapters across the U.S. to test navigability, detect problems, identify problem severity, and develop recovery strategies. In remote usability testing, researchers are in a different location than the users, but both parties are on a web conference call and are sharing screens. Researchers can see what participants are doing, and they can communicate with each other in real time. The researcher provides test participants with activities to complete while using a design or interface, and users typically think out loud as they work on the tasks. The researcher observes the user as they work through the tasks, and ask questions for clarification or to gather more data. Two key benefits of remote usability testing are that the participant is in their natural environment and gives more realistic insight than when in the lab, and it allows feedback from participants in geographically dispersed areas.[111-113] Evidence supports the use of remote usability testing as a viable approach to gather high-quality user experience feedback.[114,115] The *Pinpoint* sessions occurred over the web using Zoom videoconferencing and were approximately 1 hour in length. Participants were asked to complete defined tasks within the app, including completion of the PAT. Participants were also asked to complete the System Usability Scale (SUS).[108] The sessions were audio recorded via Zoom videoconferencing software. Similar to the cognitive interviews and focus groups, participants had to be between the age of 13 and 17 years, be diagnosed with SCD, able to speak and read English, and have parental consent to participate and assent to participate. Compensation was $30. Five participants were female (42%), and the average age was 14.6 ± 1.0. Severity in usability concern/errors are categorized into levels: Level 1 is the most severe and represents issues that make it impossible for the user to finish a task; Level 2 are programming issues that do not function ideally, but do not impede users from finishing a task; Level 3 are programming issues or tasks that do not cause a high level of concern. Level 1 severities were noted with the first usability tester, however, they were quickly debugged and did not impede with future usability testers. Level 2 and 3 issues can be easily addressed in future iterations of *Pinpoint* development. In addition to navigation and technical items, most testers reported high acceptability of visual design, functionality, and content. Overall, users thought the program would be helpful in identifying and reporting their pain. After usability testing, the testers completed the System Usability Scale (SUS),[108] a validated tool for assessing the usability and acceptability of technology-based products.[116,117] A SUS score of 68% is considered above average[108] and served as the criterion for measuring *Pinpoint's* usability. The total SUS score for the program was 86.6% suggesting a high level of acceptability and usability.

3C.1f. Phase I Aim 6. Cognitive Interviews with Providers (Appendix D). Interviews were conducted with medical providers of SCD patients (n=5) to review the app to determine whether they found it appropriate, acceptable, useful, and the content appropriate. They were also asked to respond to their interest in using *Pinpoint*, and its clinic meaningfulness. Eligibility criteria were: medical provider to SCD patients, over 18, able to speak and read English, and consent to participate. Compensation was $50. Similar procedures for remote app evaluation as presented above in the Lab Usability Testing section were used. The providers reported that the body scanner was an effective tool to guide patients through body self-reflection (avg. score of 4 out of 5); patients would learn to better self-disclose (avg. score of 4 out of 5); patients would learn new words to better describe their emotions and pain (avg. score of 4.25 out of 5); and patients would be more likely to assess their pain because of the app (avg. score of 4.66 out of 5). They thought clinic implementation could be accomplished, and liked the idea of summary pain reports provided via email, patient portal, or app.

FIGURE 4. Pinpoint Flow

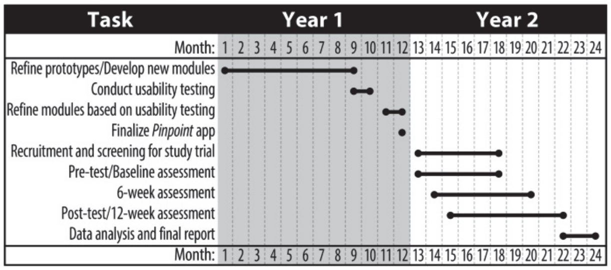


3C.1g. Phase I Aim 7. Specifications Document*.* A site map is a visual representation of the content areas of the technology program and how they relate to one another. The Specifications Document provides general program information, program progression, system architecture, and user dialogues. A site map (**Figure 4**) and Specification Document has been completed.

3C.1h. Phase I Aim 8. Importance of Results. Phase I findings show: (1) SCD teens are interested in an app that helps them communicate about their pain; (2) KB can create an app with gamification principles for SCD and communication content; and (3) participants approved of the app design and concept. The Specification Document and EAB feedback indicate it is possible to develop a full-scale app in Phase II and market potential exists.

3C.1i. Evidence for Scientific Premise. SCD is a prevalent genetic disorder with significant public health impact. Pain is its hallmark symptom and accurate pain reporting is critical to effective care. High quality research has demonstrated that children can be accurate self-reporters of pain. Yet, barriers to effective communication between SCD youths and their care team (parents, providers, etc.) still exist. Children are high utilizers of technology; gaming approaches are not only popular but have demonstrated positive health behavior effects in the mHealth literature. Despite the encouraging evidence of "games for health", the area of gamification for assessing pain, especially SCD pain, is remarkably underdeveloped despite promising results. Our proposal addresses gaps in the current literature, but is founded in strong preliminary evidence. Our Phase I research used a multi-method approach with input from key stakeholders and experts in the field. Using a user-centered design approach and social cognitive theory, we produced a functional prototype that was rated high for aesthetics and usability suggesting acceptability and feasibility of the product. Our Phase I outcomes provide strong preliminary evidence for moving forward with a full-scale production of the app.

FIGURE 5: Timeline



3C.2. Project Overview. The Phase II project will be conducted over 24 months (**Figure 5**). *Pinpoint* will be fully developed in Months 1-9 and evaluated for behavior change (i.e., increased communication skills) in Months 10-24 among a sample of teens with SCD aged 13-17 years. *Pinpoint* will be a web-based app that provides pain identification and assessment, and disease education. Using the user-centered design (UCD) approach from Phase I, usability testing will be conducted on newly programmed features (n=14) and will guide final app development. A within-subjects design will enroll teens with SCD using a time series approach. Teens will be recruited from across the U.S. through SCD support groups and networks (see **Letters of Support**), and will use the app for 12 weeks. The primary outcome will be improvements in communication skills regarding SCD. Teens (n=100) will complete baseline, 6-week, and 12-week assessments (**Figure 7**).

3C.3. Investigative Team. This project will be led by Valerie Myers, Ph.D. Dr. Myers is a Senior Scientist and licensed psychologist. She studies technological approaches to promote health among at-risk populations in real-world settings. Dr. Myers has served as a PI or Co-I on several NIH- and state-funded grants. Formerly, she was a Research Associate at Children's Hospital of Philadelphia (CHOP) and conducted psychosocial assessments and treatment with patients and families with SCD through the Sickle Cell Disease Study. Dr. Myers will be joined by Hilton Hudson, MD (Co-I) and Ms. Mary Buller, MA (Co-I). Dr. Hudson specializes in general cardiac and thoracic surgery, and has extensive medical and administrative experience at a number of agencies. In addition to practicing medicine, Dr. Hudson is President and CEO of Hilton Publishing Co. and EMIC LLC (Evidence-based Medical Information Company). He will Chair the EAB. Dr. Hudson is well-suited for his position as EAB Chair due to his SCD experience, and his experience with disseminating point-of-care tools within the medical domain. Ms. Buller has a master's degree in communication and will help guide instructional design and creation of new app content. Ms. Buller has been PI or Co-I on a number of SBIR and STTR Phase I and II projects including projects targeting under-served populations and utilizing gamification techniques. KB's Creative Team will lead the user-interface design and programming of the app. KB has extensive experience with formative research, prototype testing, and full-scale production on multiple technology interfaces and has developed a successful iterative, user-centered design process (based on the ADDIE Model,[118-120] MDA Framework,[121,122] and AGILE programming techniques[123,124]). KB has developed health behavior technologies including app and game development for children and teens, and successfully recruited and implemented technologies in pediatric clinical settings on a number of federally-funded projects.

3C.4. Technology Design and Development (AIM 1): The AIM 1 goal is to develop a fully programmed, interactive *Pinpoint* app consisting of 5 modules addressing pain identification and communication.

3C.4.1 <u>Expert Advisory Board (EAB) Guidance.</u> The EAB was instrumental in the Phase I project, and will continue to provide guidance on newly developed modules for Phase II (see **3C.4.3c**). Drs. Darbari and Hsu will continue to serve as well as Mr. Platt. A new member (Ms. Lisa Rose, M.Ed) will join the EAB. Ms. Rose is the Executive Director at HOPE for SCD, an organization that provides medical education to families and partners with local SCD community organizations. HOPE for SCD has published a book, *Sickle What?,*[125] which is a part of the *Hope and Destiny* Sickle Cell Patient Education Series. In the event that an area of expertise is needed, we will recruit an additional member. The EAB will meet a total of 6 times during the project to provide guidance on content development and recruitment (see **Letters of Support**). Dr. Hsu and Mr. Platt (both authors of *Hope and Destiny*) will also serve as Other Significant Contributors (OSCs) on the project to provide more in-depth and time-intensive content development and recruitment assistance.

3C.4.2 <u>Parent Advisory Board (PAB) Guidance.</u> During our Phase I focus group and usability testing sessions, parents expressed a strong interest in being a part of the app development as well as providing a parent perspective on communication strategies with their children. In response, a Parent Advisory Board (PAB) will be established. The PAB will provide early and frequent user-focused feedback on app design, and will meet at total of 6 times during the project period. Five parents have provided **Letters of Support**, and another five have expressed interest in participating. The inclusion of teens, SCD experts, and parents assures that we will have multiple stakeholder feedback across all phases of our project.

3C.4.3 <u>Prototype Programming.</u>

3C.4.3a <u>Theoretical Foundation, Content Translation, and Gamification.</u> *Pinpoint* content development and instructional design will be led by Dr. Myers with assistance from Ms. Buller, Dr. Hudson, EAB, and PAB. *Pinpoint* content will be drawn from the best-selling book, *Hope and Destiny, Jr.*[100] This book is the only comprehensive, culturally-sensitive book on SCD for children available on the market. Translation of content will be guided by social cognitive theory (SCT).[87] Two primary book content areas will be targeted for translation: (1) the educational content which describes SCD and its co-occurring conditions geared towards the child's perspective; and (2) the "Stories from Kids Like You" sections. The "Stories" are testimonials from youth with

SCD that are presented throughout the book and are real-life narratives regarding the different educational components presented. Book content will be categorized into SCT theoretical components, e.g., Modeling; Outcome Expectancies; Self-efficacy; and Identification. Gaming theory elements and components will be then be applied to target the SCT assumptions of: (1) people learn from others (e.g., cognitive and observational modeling presented through direct, symbolic, and synthesized models); (2) self-regulated behavior is essential to the learning process (e.g., goal-setting, self-observation, self-assessment, self-reinforcement); and (3) learning involves the interaction and reciprocal causation of multiple factors (e.g., beliefs and expectations; reinforcement). In Phase I, a sampling of the educational content and "Stories" were programmed into the app. Phase II will program additional book content.

Gamification has three primary elements: (1) **Dynamics** ("the grammar of the game") is the game content which can include such things as emotion and progression through levels to improve learning (this targets the SCT components of modeling, reciprocal causation, and outcome expectancies); (2) **Mechanics** ("the verbs of the game") drives the actions of the game forward and include such things as rewards, feedback, and challenges (this targets the SCT components of self-regulation, outcome expectancies, self-efficacy, and identification); and (3) **Components** ("the nouns of the game") are the real instances of game dynamics and mechanics and can include a number of options such as badges, leaderboards, levels, points, achievements, avatars, content unlocking, quests, social recognition, teams, and virtual goods (this targets the SCT components of modeling, outcome expectancies, self-efficacy, self-regulation, identification, and reciprocity). **Figure 6** provides an example of the use of an avatar and how it could be applied to SCD knowledge acquisition using SCT components. An avatar (i.e., "learning buddy") was a requested addition for Phase II by the EAB and the teens.

FIGURE 6: SCT with Tina, the Learning Buddy

Tina is a learning buddy that follows the user throughout the game. Interactions with Tina are used to integrate the ideas of SCT, such as modeling behavior, providing support, and encouraging user to reach pain management goals. During registration, the user chooses Tina as her learning buddy from a menu of many learning buddies.

Modeling: Tina answers a question the user picks from a list to model likely peer SCD behaviors that reach towards goals.

Check-In: Tina asks the user how she feels every time she logs on.

Setting Goals: After playing an SCD pain management game, Tina appears to show the user how to set goals and relate to the user.

Sharing: Tina shares a story with the user and then the user can choose a way to share a story back (i.e. journal, video entry).

3C.4.3b <u>App Development</u>. The design process will be informed by: (1) the ADDIE Model,[118-120] a user interface and instructional design approach; (2) the Mechanics, Dynamics, and Aesthetics (MDA) framework,[121,122] a dynamic game development process that incorporates the perspective of the researcher, developer, and user; and (3) AGILE programming, a collaborative and incremental programming methodology.[123,124] This multi-model approach is systematic, flexible, and cost-effective. It ensures that all design and programming elements are aligned and stakeholders' inputs are incorporated throughout the multi-staged development. Design elements such as **space** (colors, sounds, visual space), **components** (characters, objects), and **mechanics** (actions) will be determined for *Pinpoint's* features (i.e., assessment, activities, games, tools). App user-interface (UI) design and programming will be conducted by the KB Creative Team using similar application approaches used in Phase I (see **3C.1d**).

3C.4.3c. <u>Development of New Components.</u> The *Pinpoint* app will focus on helping SCD teens build practical and constructive communication skills and providing them with a platform for practice and feedback. Examples of communication content areas include nonverbal communication, self-disclosure, expression of emotions, trust, mutual respect, empathy, conflict management, and coping strategies. Consistent with research on mHealth strategies for adolescents,[126-130] the proposed design emphasizes gaming as a teaching strategy. These interactive components will be the centerpiece of the app. Outcomes of each game will be used to ensure uptake of information (e.g., users must achieve a targeted score or level to demonstrate comprehension to receive a reward), thus providing feedback to participants early and often. To reinforce learning and bolster adherence, "badges" (i.e., visual icons), will be awarded intermittently. Badges are highly effective gaming tools used to encourage user engagement and build game "loyalty".[131-134]

Details of components programmed in Phase I were provided in **Section 3C.1d** and **Figure 4**. Three modules were programmed in Phase I and will be refined and expanded in Phase II. Two additional modules will be built from scratch: Daily Pain Journaling and Resources for Parents, Providers, and Teens; each module will contain multiple sections. Based on Phase I feedback, the app will use an avatar to help guide and provide modeling and instruction to the user. Teens will be asked to set pain management goals (e.g., methods to maintain health, commitment to reporting pain episodes, etc.). The **Learn about Communication** module will be expanded: additional Johari window games for self-disclosure will be created and a new section (Practicing Disclosure) will include an interactive game to promote expressive communication. Additional games targeted towards improving expression of emotions and increasing trust will be included in this section. **Daily Pain Journal** will be a new module which focuses on daily self-monitoring of pain. This module will include interactions with the avatar to build skills for mutual respect, empathy, conflict management, and coping strategies. The **Pain Assessment Tool** module will be expanded to include a historical log of the pain assessments which will be housed in the app database and can be "pushed" to others (e.g., parents, providers) in an email format. The ***Hope & Destiny, Jr.*** module will include additional book content. The **Extra Resources** module will contain parent, provider, and teen information such as current trends and research in SCD. For all modules, *Pinpoint* will use media-rich activities and games with videos and other engaging tools.

3C.4.4 <u>Usability Testing (AIM 2):</u> The AIM 2 goal is to conduct usability testing of the *Pinpoint* app to evaluate the user interface, ease of use, and perceived barriers in order to optimize the app prior to large scale evaluation (n=14). The purpose of usability testing is to validate the app's design and to identify and correct problems prior to testing the app in a more systematic trial. Research suggests that at least 10 users are needed to capture 95% of most usability problems.[135-137] To identify any problems that impact $\geq$15% of users at a 90% chance of detection (log(1-.90)/log(1-.15)), 14 teens are needed.[138,139] A parent will give consent; teens will give assent. Consent and assent forms and procedures will be IRB-approved. Eligibility criteria are: a) age 13-17 years; b) diagnosed with SCD; c) own a smartphone or tablet, and d) read and speak English. Compensation will be $25. We will attempt to recruit equal numbers of males and females for diversity of gender perspectives. Sessions will be conducted remotely in a procedure similar to Phase I (see **3C.1e**). The users will complete defined tasks while being observed and complete a usability survey. They will rate their satisfaction with the app with regards to design, appeal, functionality, and navigation using Likert-type scales. This approach for assessing feasibility and appeal of technology learning has been used successfully with youths.[140] Usability will be assessed using the System Usability Scale (SUS),[141] a validated tool for assessing the usability of technology-based products.[142,143] Project staff will make notes of issues encountered during testing.

3C.5. Experimental Design (AIM 3). AIM 3 will test the full *Pinpoint* app with 13-17 year olds with SCD (n=100) using a within-subjects times series design over 12 weeks to evaluate changes in (1) knowledge acquisition for communicating about pain and types of SCD pain; (2) the Pain Assessment Tool; (3) SCD general knowledge and self-efficacy, (4) family cohesion, and (5) app usage. The primary outcome measure (knowledge acquisition for communicating about pain and types of pain) will be developed. Change in knowledge acquisition for communication relative to baseline was chosen as the primary outcome because Phase I participants strongly expressed that improving communication skills and understanding their pain were the primary reasons why teens would use the app. In addition to teens being recruited, their parent will also be recruited to complete a parent proxy version of the primary outcome measure.

3C5.1. Trial Design (n=100). A within-subjects (repeated measures) design will be used. A number of designs were considered. A comparative-effectiveness trial was rejected since there is no existing app geared for SCD teens that could act as an appropriate comparator. A randomized controlled design was contemplated, and we considered a number of possible control conditions (e.g., no treatment control, waitlist control, etc.). However, we rejected the RCT concept due to resource demands for obtaining a large sample size for sufficient power (i.e., time and cost relative to a 24-month Phase II timeline), and input from the EAB and parents. Specifically, the EAB and parents believe parents would not be interested in participating if the possibility of a control condition was present. The purpose of a Phase II grant is to continue the research and development efforts initiated in Phase I and prepare it for commercialization. Our primary goals are to fully build the app and assess for individual improvements in communication and pain identification over time. Thus, a within-subjects design was chosen. The advantages of the within-subjects design are increased power with smaller sample size, and a reduction in error variance associated with individual differences. While the lack of a control group is a limitation, it was necessitated to overcome challenges in recruiting SCD teens experienced in Phase I. We will devote project resources to recruiting and retaining a sample in the treated group (i.e., receives *Pinpoint* app) that is sufficient to detect pre-post changes in primary and secondary outcomes rather spend resources on securing a sample of which half will not be treated. We will also avoid having parents decline to participate due to the chance their teen will not receive the app. We have included two design aspects to control threats to validity[144]: (1) we have a 6-week interim measure to create a time-series on the assessment of change; and (2) we will include a measure of communication and knowledge related to influenza as a nonequivalent dependent variable, which we do not expect will change pre to post as a result of the app despite it being subject to the same history, maturation, or regression threats as our primary and secondary measures. We will also include demographics, especially age of the teen and parental age and education, as covariates in the analysis as statistical controls against threats such as maturation.

A description of the app was provided in **Sections 3C.1d** and **3C.4.3c**. Participants will download the app following the procedures outlined in **Section 3C.7.1**. Project staff will provide users with a one-on-one app orientation and how to use its unique features via videoconferencing. Daily notifications will engage users in daily app use and provide up-to-date information on users' progress. Participant responses will also be used to evaluate additional or on-going support of users' needs. To protect privacy and to ensure that the participant is the person completing the app activities, KB will uniquely identify the user's smartphone/tablet based off the device's "hardware footprint". The app will upload all app activity data to the KB secured web server database.

3C.6. Target Population. There are two populations: teens with SCD and their parent. Inclusion criteria for teens are: (a) age 13-17 years; (b) diagnosed with SCD; (c) own a smartphone or tablet, and (d) read and speak English. Parents will be recruited to complete a parent proxy version of the primary outcome measure (child's knowledge acquisition; see **3C.7.2**), but will not use the app. Parent inclusion criteria are: (a) parent/guardian of eligible child and (b) able to speak and read English.

3C.7. Trial Conduct.

3C.7.1. Recruitment and Visit Procedures.

Recruitment and Screening: Potential study participants will be recruited through nationwide SCD support groups, SCD networks, social media ads, and existing research participant databases. Recruitment was a challenge during Phase I due to IRB delays at the study hospital. Thus, we reached out to multiple national organizations to assist with Phase I recruitment. During Phase I, a number of organizations expressed interest in being a recruitment center for Phase II. We have four committed organizations and four others have expressed commitment via phone or email communication (see **Letters of Support**). In addition, we have the commitment of the EAB and PAB to assist with recruitment.

Participants will be sent an email describing the study and a link to an eligibility screening survey via KB's secure server. The online screener will take 5 minutes. Phone screening will be used as needed. Participants will receive an email informing them of eligibility. Eligible participants will be scheduled for an orientation/baseline visit which will be conducted via videoconferencing; a reminder email and text message will be sent 3 days prior to the assessment (similar reminders will be sent for 6- and 12-week visits).

Orientation and baseline/pre-test assessment: In a one-on-one orientation session to be conducted via videoconferencing, participants will have the study explained and provide written consent (parent) and assent (child). Immediately following, the teen will complete pre-test surveys online using their personal smartphone or tablet device (see **3C.8**) which should take about 30 minutes to complete. Parents will complete an online survey (proxy measure of the primary outcome). After the surveys, teens will be assisted with app download, provided instructions on how to use the app, and encouraged to use the app daily.

6-week interim assessment: Participants will complete interim assessments of initial changes (i.e., teens to complete all measures; parent to complete the single proxy measure assessing their child's knowledge acquisition). An invitation email and text messages containing a link to the surveys along with their unique password (PIN number) will be sent. Participants will complete the web-based surveys using either their tablet or smartphone; no video meeting will be required. Participants who do not complete the surveys within 3 days will receive an email and text reminder (and 3 more reminders at 3-day intervals if still not completed).

12-week post-test assessment: Participants will complete a post-test assessment via videoconference. They will meet individually with a study staff to complete the online surveys and a brief post-test interview.

3C.7.2. Outcomes: Baseline, Interim, and Post-test Measures. The baseline, 6-week interim, and 12-week post-test surveys will use a measure created by the investigative team and EAB as the primary outcome (i.e., knowledge acquisition for communicating about pain and types of pain). Secondary outcomes will be the app Pain Assessment Tool (PAT) and validated measures of SCD knowledge, disease self-efficacy, and family cohesion. Surveys should take 30 minutes to complete (see **Figure 7** and **Appendix E**).

Knowledge Acquisition (Communicating about pain and SCD pain knowledge): The primary outcome measure will be developed for this project in collaboration with the EAB, and psychometric properties for will be evaluated (e.g., content-validity, criterion-related validity, construct validity, and internal consistency) using a 3-step scale development process: (1) domain identification and item generation; (2) content expert validation, and (3) pilot test.[145] The investigative team will generate items using a sorting process that encompasses themes/construct elements noted in the communication (nonverbal communication, self-disclosure, expression of emotions, trust, mutual respect, empathy, conflict management, and coping strategies) and pain identification literature (Step 1). Items will then be subjected to expert validation by the EAB (Step 2),[145] who will identify and delete theoretically incoherent items thus ensuring that the items in the instrument demonstrate content validity. Specifically, the EAB will sort the items by "how much" each item measures its targeted construct. The comprehensiveness of the entire instrument will be evaluated by identifying items which the EAB perceives to be incongruent with its nominated domain. The EAB will then be asked to identify the clarity of each item's construction and wording to ensure that there are no ambiguous and poorly written items. Lawshe's Content Validity Ratio (CVR)[146] will be utilized to assess the content expert judgment; a minimum CVR value of 0.49 will be required for retention in the scale.[146] For Step 3, usability testers (see AIM 2) will be asked to complete the measure to guide preliminary psychometric evidence and allow for revision of the instrument prior to launching in the full study. Reporting of internal consistency reliability is a necessary part of scale development.[147] Cronbach's coefficient alpha of .70 is the suggested minimum.[148] All the factors' intercorrelations will be calculated and should be less than 1.00 to be conceptually distinct. To allow precision in evaluating the new measure, confirmatory factor analyses (CFA) will be conducted. Exploratory factor analysis (EFA) may be required depending on the results of the CFA. The overall purpose of exploratory and confirmatory factor analyses will be to ensure the stability of the factor structure.

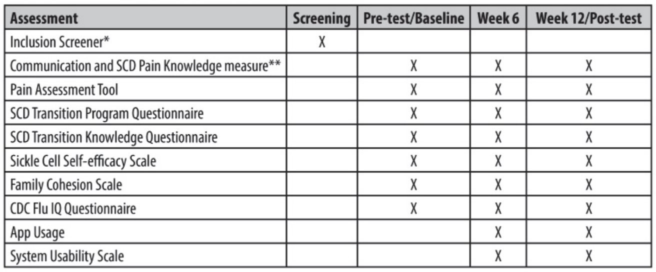
Pain Assessment Tool (PAT): The PROMIS® (Patient-Reported Outcomes Measurement Information System) is a set of self-report measures that evaluates and monitors physical, mental, and social health in adults and children. It can be used with the general population and individuals living with chronic conditions.[36] PROMIS was designed to enhance communication between clinicians and patients in diverse research and clinical settings. It was also created to be relevant across multiple health conditions for the assessment of symptoms and functions. The PROMIS Pediatric multisite initiative created pediatric self-report scales measuring the unidimensional health attributes of depressive symptoms, anxiety, anger, pain interference, peer relationships, fatigue, physical functioning - mobility, physical functioning - upper extremity, and asthma.[149] The PROMIS pediatric measures have been validated in a variety of illnesses experienced by children including cancer, kidney disease, and obesity.[150] Only one study has examined PROMIS in SCD children and preliminary results show that the measures are feasible and valid.[50] To date, there have been no studies that have gamified the PROMIS measures. In Phase I, the following PROMIS questionnaire banks were gamified and usability tested: Family Relationships, Physical Activity, Physical Stress Experiences, Strength Impact, Pain Behavior, Pain Quality-Sensory, and Pain Quality-Affective. These same domains will be refined in Phase II and serve as secondary outcomes in the trial. In addition, we will gamify the Pain Interference, Psychological Stress Experiences, and Peer Relationships domains (per EAB recommendation in Phase I).

SCD Knowledge: SCD knowledge will be measured using two scales. The SCD Transition Program questionnaire[151] is a reliable 10-item measure developed from the Stepping Up to Adult Care Program.[152] Content areas covered include the etiology, clinical manifestations, and medical management of SCD. Higher scores indicate better knowledge of SCD and its treatment. The *SCD Transition Knowledge Questionnaire*[153] is a 25-item multiple-choice measure that assesses knowledge of SCD relevant to preparation for transition to adult services. It is designed to assess SCD knowledge in seven areas: (1) pathophysiology, (2) genetics, (3) physical symptoms, (4) treatment, (5) self-care, (6) psychosocial and developmental issues, and (7) health care delivery. It has good psychometric properties.[153,154] Higher scores represent greater knowledge.

Sickle Cell Self-efficacy Scale: This instrument, used to assess self-efficacy in adolescents with SCD,[155] is comprised of nine questions measuring participants' perceptions of their ability to function on a day-to-day basis and to manage SCD symptoms (e.g., pain). The instrument is reliable and valid for assessing adolescents' self-efficacy for engaging successfully in day-to-day activities despite having SCD.

Family Cohesion: Family cohesion will be assessed by the single item Family Cohesion scale from the Child Health Questionnaire (CHQ)[156], a pediatric quality of life (QOL) survey that has been normed for children age 5 to 18 years including those with chronic diseases. The CHQ consists of 28 items that assess 14 different concepts regarding child and family physical and psychosocial well-being. There is evidence of good reliability and validity of this measure[156] including the single-item Family Cohesion question.[157] This scale, which rates a family's ability to get along with one another, uses a single item ("In general, how would you rate your family's ability to get along with one another?") rated on a 5-point scale. The PAT is assessing QOL, therefore to reduce duplication of information and study burden only the Family Cohesion item will be administered.

FIGURE 7: Schedule of Measurements



Assessment	Screening	Pre-test/Baseline	Week 6	Week 12/Post-test
Inclusion Screener*	X			
Communication and SCD Pain Knowledge measure**		X	X	X
Pain Assessment Tool		X	X	X
SCD Transition Program Questionnaire		X	X	X
SCD Transition Knowledge Questionnaire		X	X	X
Sickle Cell Self-efficacy Scale		X	X	X
Family Cohesion Scale		X	X	X
CDC Flu IQ Questionnaire		X	X	X
App Usage			X	X
System Usability Scale			X	X

* Completed by parent only
** Completed by teen and parent

CDC Flu IQ measure: This is a 10-item quiz developed by the Centers for Disease Control to assess general knowledge about influenza and vaccination. It will serve as a nonequivalent dependent variable.

App Usage: App use will be monitored using Web Trends software; tracking macro and micro level data. It will record how users move through the program including the time spent on each activity, response latency to individual items, and scores achieved on games. Summaries of these data (means, ranges) will be reviewed to understand usage patterns. Teens will be sent "push notifications" to encourage app use. Users will evaluate the app on the **System Usability Scale** at the 6- and 12-week assessment.[142]

3C.7.3. Adherence, Dropouts, and Participant Compensation.

Retention, Tracking, and Attrition: Although participants can withdraw at any time, steps will be used to minimize dropouts to ensure high internal validity. Participant progression will be tracked. Staff will use behavioral reinforcement strategies known to be effective in the behavior change literature[158-160] and be trained to develop rapport with participants by communicating expectations for participants and staff. Personalizing this relationship will enable participants to be more direct about problems, providing a strong foundation for problem-solving. While drop-out rates vary among youths with SCD,[57,161] we conservatively planned for 20% attrition. Our method of tracking and multiple contacts will help us retain some of these participants for intent-to-treat purposes, despite their discontinued app use. Participants will provide contact information for one individual who can always contact them and update contact information at each assessment. If they do not respond to email/text reminders, we will follow-up by phone. Finally, we will create a dummy coded variable for each respondent where 1=completers and 2= drop outs and test for associations with key variables in our analytic models. If bias is identified, we will control for it by adding it as a covariate.

Compensation: All participants (n=100) will be compensated to incentivize and improve study retention. A $20 gift card will be given to the teens after each study assessment (baseline, 6-week, and 12-week) for a total compensation of $60. Parents will be provided a $10 gift card after each study assessment for a total of $30.

App Use: Implementation of technology-based interventions can be challenging due to participants forgetting, fatiguing, or believing they have learned all they need to know. In order to bolster compliance with using either of the assigned app, weekly reminders to use the app will be sent to participants by text message.

3C.7.4. Safety Considerations. Participant safety is a priority. This study will include a Data and Safety Monitoring Plan (DSMP). The team will monitor progress, discuss concerns, and take corrective actions. Dr. Myers (PI) is a licensed psychologist and will assemble a group of experts including at least one licensed mental health professional, physician, and biostatistician. Participants who express emotional or physical distress will be referred to their treating physician immediately. Based on our experience and demonstrated ability to conduct this type of research, we are confident we can achieve safe intervention delivery.

3C.8. Data Collection, Management, and Security. KB has used online data collection successfully in a number of studies. Study consents and pretests and posttests will be collected online via participants' personal smartphone or tablet. Surveys will be programmed using QuestionPro software on KB's secure web server to ensure a structured approach and reduce errors/missing values. All procedures will be approved by KB's IRB.

KB has considerable experience maintaining large databases and ensuring high-quality data. Ms. Lucia Liu, KB's Biostatistical Manager, will supervise data management. All data will be uploaded in real-time using KB's secured network; data will be de-identified and stored in KB's secured database. Established KB protocols for quality assurance (valid ranges; internal consistency checks, etc.) will ensure high quality data. The KB data team will compile master data files. Survey and app usage data will be linked. Missing data should be limited since data is recorded electronically. Staff will identify missing responses and check that entries were not intentionally skipped. Analyses will be done on data collected. While unlikely, data may not be missing at random (NMAR). KB will assign all lost responses to extreme category and perform multiple imputation procedures that can handle various amounts of missing data and use covariates and propensity scores.

Data security: KB's server farm has 5 Dell PowerEdge servers with two 3.2 Ghz Xeon processors, four with 32 gigabytes of RAM and one with 64 gigabytes, and three 1 Terabyte hard drives that operate off a hardware RAID5 system, connected to a local area network (LAN) running the Windows 2008 or 2012 operating system and to the Internet through a 20-megabyte Fiber connection. KB programmers monitor and maintain all programs and databases. Sensitive information is protected by a hardware firewall (Cisco ASA 5505) and each server has its own native Windows security software. All KB servers are connected via 1 Gigabit high-speed switched network, ensuring high-speed transfer between machines. All networked computers are protected from viruses by Sunbelt Vipre Enterprise. Nightly backup of each computer protects against data loss.

C.10. Evidence for Scientific Rigor and Potential Limitations. The study has numerous strengths, few limitations, and is scientifically rigorous. The study is theory-driven (i.e., User-centered Design and Social Cognitive theories). Formative data will incorporate multiple stakeholder input. The programming approach will be multi-model and evidence-based (i.e., ADDIE Model, MDA framework, AGILE programming) resulting in a systematic, flexible, and cost-effective approach. Sample sizes are sufficient and supported by the literature. Effectiveness will be evaluated in a within-subjects design which allows for sufficient power (i.e., statistical inference with fewer subjects), efficiency (i.e., quicker trial completion), and longitudinal analysis (i.e., individual changes over time). The study team and environment are strong. Potential limitations are: (1) difficulty recruiting; (2) sources of bias; and (3) lack of control group. We have tried to reduce their impact. We will work closely with the EAB and PAB to maximize recruitment. Our primary outcome measure is new, but we are using a rigorous approach to scale development. Self-report instruments are open to bias, however the use of validated measures are a strength. Limitations of no control group are lessened via the use of a time-series design for outcome changes and use of a nonequivalent dependent variable.

5. PROTECTION OF HUMAN SUBJECTS

5A. Risks to Subjects

5A.1. Human Subjects Involvement, Characteristics, and Design. The proposed research involving human subjects will be conducted by Klein Buendel, Inc. (KB: FWA No. 00003715).

The subject population for this study will be teens with Sickle cell disease (SCD) and their parent. Participants will consist of both males and females and participants will be of African American, Hispanic, and white race/ethnicity. All participants will be asked to complete a demographics form. The demographics are detailed in Section 7 and the Targeted Enrollment Table.

Human Subjects will include:

1. Usability Testing Participants (n = 14) will evaluate the user interface, ease of use, and perceived barriers in order to optimize the app prior to large scale evaluation. The purpose of usability

testing is to validate the app's design and to identify and correct problems prior to the evaluation period. A parent will give consent; teens will give assent. Consent and assent forms and procedures will be IRB-approved. Eligibility criteria are: a) age 13-17 years; b) diagnosed with SCD; c) own a smartphone or tablet, and d) read and speak English. Compensation will be $25.

2. Evaluation Period Participants (n=100) will test the full *Pinpoint* app using a within-subjects pre-post design over 12 weeks to evaluate changes in (1) knowledge acquisition for communicating about pain and types of SCD pain; (2) the Pain Assessment Tool; (3) SCD general knowledge and self-efficacy; (4) family cohesion; and (5) app usage. A parent will give consent; teens will give assent. Consent and assent forms and procedures will be IRB-approved. Eligibility criteria are: a) age 13-17 years; b) diagnosed with SCD; c) own a smartphone or tablet, and d) read and speak English. Participants will use the app for 12 weeks after a one-on-one orientation to the app where teens will be assisted with app download, provided instructions on how to use the app, and encouraged to use the app daily. Participants will complete a baseline, a 6-week, and a 12-week assessment. Participants will be compensated to incentivize and improve study retention. A $20 gift card will be given to the teens after each study assessment (baseline, 6-week, and 12-week) for a total compensation of $60.
3. Parent Online Survey participants (n=100) will complete an online survey at the baseline, 6-week, and 12-week assessment. Parent inclusion criteria are: (a) parent/guardian of eligible child and (b) able to speak and read English. Parents will be provided a $10 gift card after each study assessment for a total of $30.

5A.2. Sources of Research Material. Data from the usability testing will be collected in the form of handwritten notes, audio tapes, computer files, transcriptions and questionnaires. Transcripts of audiotaped discussions will be analyzed via Atlas-ti© content and thematic analysis software to identify consistent and recurrent content and themes in response to discussions. Data gathered from the usability testing will be summarized in notes by research staff to identify usability problems.

Participants (teens and parents) will complete a baseline, a 6-week, and a 12-week assessment during the evaluation period. Data gathered from the questionnaires and surveys will be collected online, using KB's online survey software, QuestionPro®. App usage will be monitored using Web Trends software. All data will be obtained specifically for research purposes. Access to all data will be limited to the Principal Investigator (PI), Co-Investigators, specific project staff, and consultants. Data will be kept confidential and anonymous and will be kept in locked files and secure servers.

5A.3. Potential Risks. There are minimal risks associated with participation in this study. The potential risks in this project are limited to minimal psychological risks. Participation in the usability testing, which requires children to answer general usability questions about the *Pinpoint* tablet app, has slight risks. Participants may be hesitant or uncomfortable responding to questions about their opinions regarding the *Pinpoint* tablet app.

Participation in the evaluation period and the parent online surveys has minimal risks. Participants may be hesitant to answer questions related to (1) knowledge acquisition for communicating about pain and types of SCD pain; (2) the Pain Assessment Tool; (3) SCD general knowledge and self-efficacy, (4) family cohesion, and (5) app usage. All responses collected in this project will not be shared with anyone except project staff. All participants will be allowed to withdraw from the project at any time.

5B. Adequacy of Protection Against Risks

5B.1. Recruitment and Informed Consent. Human Subjects oversight will be conducted by Western Institutional Review Board (WIRB; DHHS IRB Reg. No. 00000533). WIRB will review and approve subject materials (including recruitment materials, consent forms, and survey instruments) and data management procedures prior to study implementation.

Potential study participants will be recruited primarily through nationwide SCD support groups, SCD networks, social media ads, and existing research participant databases. In addition, we have the commitment of the EAB and PAB to assist with recruitment.

For the usability testing, children participants will view the app and provide feedback about its user interface, ease of use, and perceived barriers. Usability testing sessions will be conducted remotely. In remote usability testing, researchers are in a different location than the users, but both parties are on a web conference call and are sharing screens. Researchers can see what participants are doing, and they can communicate with each other in real time. The researcher provides test participants with activities to complete while using a design or interface, and users typically think out loud as they work on the tasks. The researcher observes the user as they work through the tasks, and ask questions for clarification or to gather more data. The users will complete defined tasks while being observed and complete a usability survey. They will rate their satisfaction with the app with regards to design, appeal, functionality, and navigation using Likert-type scales. Project staff will make notes of issues encountered during testing. Usability testing participants will be asked for assent and parental consent to participate in the usability testing. Consent/assent will be obtained using the procedures below.

For evaluation period, participants will be sent an email describing the study and a link to a screening survey administered on KB's secure server that assesses inclusion criteria and demographic characteristics. The online screener will take about five minutes to complete. If needed, phone recruitment and screening will also be used. After being screened, participants will receive an email to inform them of their eligibility status. Eligible participants will be scheduled for an orientation and baseline assessment, which will be conducted via videoconferencing. Participants will have the study explained and provide online consent (parent) and assent (child). After providing consent and assent, participants will attend a one-on-one orientation. During the orientation, teens will be assisted with app download, provided instructions on how to use the app, and encouraged to use the app daily. Then the baseline assessment session will be conducted via videoconferencing Participants will complete the (online) baseline survey(s) using their personal smartphone or tablet device, which should take about 30 minutes to complete.

Participants will complete a 6-week assessment of initial changes. An invitation email and text messages containing a link to the survey(s) along with their unique password (PIN number) will be sent. Participants will complete the online survey(s) using either their tablet or smartphone; no videoconferencing will be required for the 6-week assessment.

Participants will complete a 12-week post-test assessment. Participants will meet individually with study staff via videoconference to complete the online survey(s) and a brief post-test interview.

Consenting/Assent procedures are as follows:

A parent will be present and give consent for the child during the videoconference. Children will provide assent. Eligible children will be invited to participate, consented/assented using the following procedures:

1. Research staff will send an introductory email inviting eligible parents and children to participate and follow-up with emails and telephone calls to recruit them.
2. Interested parents will go to the study website to register and complete an online enrollment form, providing contact information (i.e., name, address, telephone numbers [home and mobile phones], and email address[es]) for themselves, their child, and people who can always locate them and their child (i.e., a locator).
3. Each parent and child will sign online consent form/assent form at the study website. If a parent or child does not consent/assent the child will not be enrolled. Participants will give their consent/assent electronically and be able to download and save (or print) a copy of the consent/assent form. The IRB-approved consent/assent forms will describe the purpose of the project, risks and benefits, and selection criteria. Participants will be informed that they have a right to withdraw from the study at any time. No additional data will be collected from participants who decide to withdraw; however, the information collected prior to withdrawal will remain in the study. All correspondence will contain the PIs' email addresses and phone numbers for invited participants to use if they have questions.

Participation in all stages of this Phase II application is entirely voluntary and subjects are free to withdraw from the project at any time without negative consequences. Furthermore, withdrawing from the study will not affect the participants' benefits. No additional data will be collected from participants who decide to withdraw; however, the information collected prior to withdrawal will remain in the study.

5B.2. Protection Against Risk. To minimize potential psychological risk, usability testing facilitators/ interviewers will establish ground rules for discussion that includes an open, non-evaluative exchange of comments and ideas. IRB-approved discussion procedures will be carried out under the supervision of senior project staff. Participants will be told that they do not have to answer any questions that make them uncomfortable and can terminate their participation at any time they wish. Notes, surveys, and data will be accessible only by research personnel. Data forms and computer records will be labeled only with participant identification number. Participant names and study identification numbers will be recorded and stored separately from the research data files.

Any survey questions and discussion transcripts will be de-identified before being submitted for analysis and the Research Assistant will remove any references to individual names or identifier data. There are no clinical data to be captured. Responses to survey questions and participation in discussions will not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation. The data collected on this project will be obtained with the "use of educational tests, survey questions and interview procedures."

To protect privacy and to ensure that the participant is the person completing the app activities, KB will uniquely identify the user’s smartphone/tablet based off the device’s “hardware footprint”. The app will upload all app activity data to the KB secured web server database.

All surveys and data collection forms will be IRB-approved and administered under the supervision of senior project staff. Participants will be told that they do not have to answer any questions which make them uncomfortable and can terminate their participation at any time they wish. Notes, surveys, and data will be accessible only by research personnel. All notes will be stored in locked cabinets; all electronic data files will be stored on KB’s secure network servers behind computer firewalls, with routine backup. All identifiers will be stored in secure files and behind computer firewalls and results will be shared in aggregate form only.

The *Pinpoint* app and databases will be hosted on KB’s state-of-the-art web server farm. Its Live and Test web servers consist of Windows 2003, Internet Information Server 6.0, dual 2.8 Ghz Processors, 4 Ghz Ram, and 120 Gb Hard Drive space. The SQL Server consists of Windows 2003, Microsoft SQL 2000, 2.8 Ghz Processor, 3 Gb Ram and 240 Gb of hard drive space configured with RAID 5. File sharing and print serving is accomplished through a Windows 2003 dual 3.2 Ghz processor server with 4 Gb RAM and 750 Gb of hard drive space configured with RAID 5. All computers are protected by Norton Corporate Edition Antivirus software. Nightly backup protects against loss of data. Three T1 lines provide Internet access. Usage is monitored with Web Trends to ensure that the server hardware and T1 Internet service is sufficient for the number of hits (and upgraded as necessary). Information stored on KB’s web server is protected by a hardware firewall (Cisco PIX); each server has native Windows security software. All the KB servers are connected via 1 Gigabit high speed switched network.

5C. Potential Benefits of the Proposed Research to Participants and Others

The benefits of this research are substantially greater than any risks. Potential benefits for all participants will be the knowledge that one has helped to evaluate a web based application that engages adolescent sickle cell disease patients in precision pain management.

5D. Importance of the Knowledge to be Gained

SCD is the most common inherited blood disorder in the U.S.,[1] and affects 70,000 to 100,000 individuals, primarily African Americans and Hispanics.[2-4] SCD causes serious and life-threatening comordities such as organ failure, acute chest syndrome, and stroke.[7,8] Pain is the hallmark symptom.[9]

Pinpoint will be the first app to identify and translate specific pain types for SCD into a gamified app using applied gamification principles while also instructing teens on how to effectively communicate their pain to others. *Pinpoint* also has strong clinical significance. It has the potential to be utilized in tandem with any pediatric care setting and can potentially reduce barriers to obtaining children’s self-report by using a medium that they are comfortable with and enjoy, while providing important pain information that affect treatment choices and overall health.

5F. Training in the Ethical Conduct of Research with Human Subjects

The Principal Investigator, Co-Investigators, and all study personnel have completed the required training in the Ethical Conduct of Research with Human Subjects. Necessary documentation will be provided to NIH prior to funds being awarded.

5G. HIPAA Research Authorization

Although we will not be collecting medical information or Protected Health Information, we may email the app content to physicians.

6. DATA AND SAFETY MONITORING PLAN

A data safety and monitoring plan will be implemented for this project, following well-established procedures within KB. We will not set up an independent Data Safety and Monitoring Board because this trial is very low risk; does not include use of therapeutics; and physical risks are not anticipated. However, the progress of the research will be monitored monthly by the PI. All critical events will be reviewed by the Investigator to ensure that project methods have not been intrusive or disruptive.

The team will monitor progress, discuss concerns, problem-solve, and take corrective actions. Dr. Myers (PI) is a licensed psychologist in Colorado (#3630) and Louisiana (#1197) and will assemble a group of experts including at least one licensed mental health professional, one physician, and one biostatistician. Participants who express emotional or physical distress will be referred to their treating physician immediately. Based on our experience and demonstrated ability to conduct this type of research, we are confident we can achieve safe intervention delivery.

The data management staff will attend regular project meetings with the PI and other project staff and routinely report on the quality of the data and other outcomes of this monitoring process. Annual reports on data safety and monitoring are submitted to WIRB.

Compliance with data collection protocols will be monitored throughout data collection by the Investigators. The Investigators are responsible for reporting all adverse events to the IRBs. Only Grade 1 events are expected on this trial. Thus, adverse events will be reported annually, as required by DHHS. This report will be reviewed by WIRB. Any action taken by the IRBs or project investigators resulting in a temporary or permanent suspension of the trial will be communicated immediately by the PI to the grant program officer.

7. INCLUSION OF WOMEN AND MINORITIES

Females and minorities (African Americans and Hispanics) will be included in this research as part of the sample of patient participants.

SCD rates in African Americans and Hispanics are far higher than in Whites. It is estimated that SCD affects to 100,000 Americans. Sickle cell disease occurs in approximately 1 in 365 African Americans; 1 in 16,300 Hispanics, and nearly 1 in 400,000 Whites. Thus, the sample of participants in the proposed research will contain the following 3 racial/ethnic groups: Black, Hispanic, and White. We will attempt to recruit: 97% African American; 2% Hispanic (any race); and 1% White.

During the recruitment process, the Project Coordinator will screen for participants using IRB-approved protocols for screening based on gender, race, and ethnicity. If the Project Coordinator finds that we are over-recruiting a particular gender or racial or ethnic group, we will place them on a waiting list until we have recruited an adequate number of targeted participants. See Targeted Enrollment Table.

8. INCLUSION OF CHILDREN

All usability testing participants (n=14) and the evaluation period participants (n=100) will be children between the ages of 13 and 17. Thus, this study is in compliance with NIH Policy for the inclusion of children. Both parental consent and child assent will be required.

References

1. Sickle cell disease. Genetics Home Reference Web site. Available at: http://ghr.nlm.nih.gov/condition/sickle-cell-disease. Published 2012. Updated August 2012. Accessed March 5, 2015, 2015.
2. Sickle cell disease (SCD): facts about sickle cell disease. Centers for Disease Control and Prevention Web site. Available at: http://www.cdc.gov/ncbddd/sicklecell/facts.html. Published 2014. Updated January 16, 2014. Accessed March 5, 2015, 2015.
3. Brawley OW, Cornelius LJ, Edwards LR, et al. National Institutes of Health Consensus Development Conference Statement: hydroxyurea treatment for sickle cell disease. *Annals of Internal Medicine.* 2008;148(12):932-938.
4. Stinson J, Naser B. Pain management in children with sickle cell disease. *Paediatr Drugs.* 2003;5(4):229-241.
5. Cope A, Darbyshire PJ. Sickle cell disease, update on management. *Paediatrics and Child Health.* 2013;23(11):480-485.
6. Mukerji I. About sickle cell disease. Sicklecellinfo.net Web site. Available at: http://www.sicklecellinfo.net/index.htm. Published 2004. Updated March 5, 2004. Accessed March 5, 2015, 2015.
7. Bhagat VM, Baviskar SR, Mudey AB, Goyal RC. Poor health related quality of life among patients of sickle cell disease. *Indian Journal of Palliative Care.* 2014;20(2):107-111.Pmc4129996
8. Schnog JB, Duits AJ, Muskiet FA, ten Cate H, Rojer RA, Brandjes DP. Sickle cell disease; a general overview. *Neth J Med.* 2004;62(10):364-374.
9. Ameringer S, Elswick RK, Jr., Smith W. Fatigue in adolescents and young adults with sickle cell disease: biological and behavioral correlates and health-related quality of life. *Journal of Pediatric Oncology Nursing.* 2014;31(1):6-17.Pmc3982311
10. Bakshi N, Stinson J, Ross D, et al. Development, content validity and user review of a web-based multi-dimensional pain diary for adolescent and young adults with sickle cell disease [published online ahead of print 2015/01/08]. *Clinical Journal of Pain.* 2015 doi: doi: 10.1097/ajp.0000000000000195
11. Ballas SK, Gupta K, Adams-Graves P. Sickle cell pain: a critical reappraisal. *Blood.* 2012;120(18):3647-3656.
12. Ballas SK, Smith ED. Red blood cell changes during the evolution of the sickle cell painful crisis. *Blood.* 1992;79(8):2154-2163.
13. National Heart Lung and Blood Institute; National Institutes of Health. The management of sickle cell disease. 2002.
14. Beyer JE, Simmons LE, Woods GM, Woods PM. A chronology of pain and comfort in children with sickle cell disease. *Archives of Pediatrics and Adolescent Medicine.* 1999;153(9):913-920.
15. Jenerette CM, Brewer CA, Ataga KI. Care seeking for pain in young adults with sickle cell disease. *Pain Management Nursing.* 2014;15(1):324-330.
16. Dampier C, Ely B, Brodecki D, O'Neal P. Characteristics of pain managed at home in children and adolescents with sickle cell disease by using diary self-reports. *The Journal of Pain.* 2002;3(6):461-470.
17. Schatz J, Schlenz A, McClellan CB, et al. Changes in coping, pain and activity following cognitive-behavioral training: a randomized clinical trial for pediatric sickle cell disease using smartphones. *Clinical Journal of Pain.* 2015;31(6):536-547.
18. Dampier C, Lieff S, LeBeau P, et al. Health-related quality of life in children with sickle cell disease: a report from the Comprehensive Sickle Cell Centers Clinical Trial Consortium. *Pediatric Blood & Cancer.* 2010;55(3):485-494.Pmc2911637

19. Crandall M, Savedra M. Multidimensional assessment using the adolescent pediatric pain tool: a case report [published online ahead of print 2005/08/09]. *J Spec Pediatr Nurs.* 2005;10(3):115-123. doi: 10.1111/j.1744-6155.2005.00023.x
20. Franck LS, Treadwell M, Jacob E, Vichinsky E. Assessment of sickle cell pain in children and young adults using the Adolescent Pediatric Pain Tool. *Journal of Pain and Symptom Management.* 2002;23(2):114-120.
21. Lopez G, Liles DK, Knupp CL. Edmonton symptom assessment system for outpatient symptom monitoring of sickle cell disease. *Southern Medical Journal.* 2014;107(12):768-772.
22. Panepinto JA, O'Mahar KM, DeBaun MR, Loberiza FR, Scott JP. Health-related quality of life in children with sickle cell disease: child and parent perception. *British Journal of Haematology.* 2005;130(3):437-444.
23. Shah N, Jonassaint J, De Castro L. Patients welcome the sickle cell disease mobile application to record symptoms via technology (SMART) [published online ahead of print 2014/02/12]. *Hemoglobin.* 2014;38(2):99-103. doi: doi: 10.3109/03630269.2014.880716
24. Beyer JE. Judging the effectiveness of analgesia for children and adolescents during vaso-occlusive events of sickle cell disease. *Journal of Pain and Symptom Management.* 2000;19(1):63-72.
25. eMarketer. Teens' ownership of smartphones has surged. July 5, 2016. https://www.emarketer.com/Article/Teens-Ownership-of-Smartphones-Has-Surged/1014161. Accessed January 2, 2017.
26. Growing Wireless. Kids wireless use facts. Growing Wireless Web site. Available at: http://www.growingwireless.com/get-the-facts/quick-facts. Accessed December 31, 2017.
27. Salen K. Gaming literacies: a game design study in action. *Journal of Educational Multimedia and Hypermedia.* 2007;16(3):301-322.
28. National Association for the Education of Young Children, Fred Rogers Center for Early Learning, Children's Media. Technology and interactive media as tools in early childhood programs serving children from birth through age 8. Available at: http://issuu.com/naeyc/docs/ps_technology_issuu_may2012?e=2112065/2087657. Published 2012.
29. Moeller B, Reitzes T. Integrating technology with student-centered learning. A report to the Nellie Mae Education Foundation. 2011
30. Noeth RJ, Volkov BB. Evaluating the effectiveness of technology in our shools: ACT policy report. *ACT Website.* 2004
31. Nicholson S. A user-centered theoretical framework for meaningful gamification. Paper presented at: Games+Learning+Society 8.0; June 2012; Madison, WI. http://scottnicholson.com/pubs/meaningfulframework.pdf. Accessed March 31, 2015.
32. Deterding S, Sicart M, Nacke L, O'Hara K, Dixon D. Gamification: using game-design elements in non-gaming contexts. Paper presented at: ACM CHI Conference on Human Factors in Computing Systems; May 7-12 2011.
33. Deterding S, Dixon D, Khaled R, Nacke L. From game design elements to gamefulness: defining gamification. 2011. Accessed 2011/09/28/.
34. Palmer D, Lunceford S, Patton AJ. The engagement economy: how gamification is reshaping businesses. *Deloitte Review.* 2014
35. Herger M. An overview of gamification in healthcare and fitness. *Enterprise Gamification Web site.* 2013
36. HealthMeasures. PROMIS. HealthMeasures Web site. Available at: http://www.healthmeasures.net/explore-measurement-systems/promis. Accessed December 28, 2017.
37. Sickle cell disease (SCD): data and statistics. Centers for Disease Control and Prevention Website. Available at: http://www.cdc.gov/NCBDDD/sicklecell/data.html. Updated August 31, 2016. Accessed November 20, 2017.

38. Sickle-cell disease and other haemoglobin disorders. Fact Sheets. World Health Organization Web site. Available at: http://www.who.int/mediacentre/factsheets/fs308/en/. Published 2011. Updated January 2011. Accessed March 6, 2015, 2015.
39. Ballas SK. Current issues in sickle cell pain and its management. *Hematology: The Education Program of the American Society of Hematology.* 2007:97-105.
40. Sickle cell disease (SCD): complications and treatments. Centers for Disease Control and Prevention Web site. Available at: http://www.cdc.gov/ncbddd/sicklecell/treatments.html. Published 2015. Updated February 18, 2015. Accessed March 5, 2015, 2015.
41. Fosdal MB. Perception of pain among pediatric patients with sickle cell pain crisis. *Journal of Pediatric Oncology Nursing.* 2015;32(1):5-20.
42. Fosdal MB, Wojner-Alexandrov AW. Events of hospitalization among children with sickle cell disease. *Journal of Pediatric Nursing.* 2007;22(4):342-346.
43. Shapiro BS, Dinges DF, Orne EC, et al. Home management of sickle cell-related pain in children and adolescents: natural history and impact on school attendance. *Pain.* 1995;61(1):139-144.
44. Ballas SK. The sickle cell painful crisis in adults: phases and objective signs. *Hemoglobin.* 1995;19(6):323-333.
45. Dobson CE, Byrne MW. Original research: using guided imagery to manage pain in young children with sickle cell disease. *American Journal of Nursing.* 2014;114(4):26-36; test 37, 47.
46. Wilson BH, Nelson J. Sickle cell disease pain management in adolescents: a literature review. *Pain Management Nursing.* 2015;16(2)
47. Akinola NO, Stevens SM, Franklin IM, Nash GB, Stuart J. Rheological changes in the prodromal and established phases of sickle cell vaso-occlusive crisis. *British Journal of Haematology.* 1992;81(4):598-602.
48. Heath LE, Heeney MM, Hoppe CC, et al. Successful utilization of an electronic pain diary in a multinational phase 3 interventional study of pediatric sickle cell anemia. *Clinical Trials.* 2017;14(6):563-571. doi: 10.1177/1740774517723307
49. Bakshi N, Smith ME, Ross D, Krishnamurti L. Novel metrics in the longitudinal evaluation of pain data in sickle cell disease. *Clinical Journal of Pain* 2017;33(6):517-527. doi: 10.1097/ajp.0000000000000431
50. Dampier C, Barry V, Gross HE, et al. Initial evaluation of the pediatric PROMIS(R) health domains in children and adolescents with sickle cell disease. *Pediatric Blood and Cancer.* 2016;63(6):1031-1037. doi: 10.1002/pbc.25944.PMC4833539
51. Haywood C, Jr., Tanabe P, Naik R, Beach MC, Lanzkron S. The impact of race and disease on sickle cell patient wait times in the emergency department. *American Journal of Emergency Medicine.* 2013;31(4):651-656. doi: 10.1016/j.ajem.2012.11.005.PMC3608692
52. Sporrer KA, Jackson SM, Agner S, Laver J, Abboud MR. Pain in children and adolescents with sickle cell anemia: a prospective study utilizing self-reporting. *American Journal of Pediatric Hematology/Oncology.* 1994;16(3):219-224.
53. Dampier C, Ely E, Brodecki D, O'Neal P. Home management of pain in sickle cell disease: a daily diary study in children and adolescents. *Journal of Pediatric Hematology/Oncology.* 2002;24(8):643-647.
54. Thompson RJ, Jr., Gil KM, Burbach DJ, Keith BR, Kinney TR. Psychological adjustment of mothers of children and adolescents with sickle cell disease: the role of stress, coping methods, and family functioning. *Journal of Pediatric Psychology.* 1993;18(5):549-559.
55. Pinquart M, Shen Y. Behavior problems in children and adolescents with chronic physical illness: a meta-analysis. *Journal of Pediatric Psychology.* 2011;36(9):1003-1016. doi: 10.1093/jpepsy/jsr042
56. Unal S, Toros F, Kutuk MO, Uyaniker MG. Evaluation of the psychological problems in children with sickle cell anemia and their families. *Pediatric Hematology and Oncology.* 2011;28(4):321-328. doi: 10.3109/08880018.2010.540735

57. Anie KA, Green J. Psychological therapies for sickle cell disease and pain (Review). *Cochrane Database of Systematic Reviews.* 2015(5):34. doi: 10.1002/14651858.CD001916.pub3
58. Edwards LY, Edwards CL. Psychosocial treatments in pain management of sickle cell disease. *Journal of the National Medical Association.* 2010;102(11):1084-1094.
59. Rebok G, Riley A, Forrest C, et al. Elementary school-aged children's reports of their health: a cognitive interviewing study. *Quality of Life Research.* 2001;10(1):59-70.
60. Varni JW, Limbers CA, Burwinkle TM. How young can children reliably and validly self-report their health-related quality of life?: an analysis of 8,591 children across age subgroups with the PedsQL 4.0 Generic Core Scales. *Health and Quality of Life Outcomes.* 2007;5(1):1.
61. Petersson C, Simeonsson RJ, Enskar K, Huus K. Comparing children's self-report instruments for health-related quality of life using the International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY). *Health and Quality of Life Outcomes.* 2013;11(1):75.
62. Tieffenberg JA, Wood EI, Alonso A, Tossutti MS, Vicente MF. A randomized field trial of acindes: a child-centered training model for children with chronic illnesses (asthma and epilepsy). *Journal of Urban Health.* 2000;77(2):280-297. doi: 10.1007/BF02390539
63. Runeson I, Hallstrom I, Elander G, Hermeren G. Children's participation in the decision-making process during hospitalization: an observational study. *Nursing Ethics.* 2002;9(6):583-598.
64. de Winter M, Baerveldt C, Kooistra J. Enabling children: participation as a new perspective on child-health promotion. *Child: Care, Health and Development.* 1999;25(1):15-23.
65. Vetter TR, Bridgewater CL, McGwin G, Jr. An observational study of patient versus parental perceptions of health-related quality of life in children and adolescents with a chronic pain condition: who should the clinician believe? *Health and Quality of Life Outcomes.* 2012;10:85.
66. Cremeens J, Eiser C, Blades M. Factors influencing agreement between child self-report and parent proxy-reports on the Pediatric Quality of Life InventoryT 4.0 (PedsQLT) generic core scales. *Health and Quality of Life Outcomes.* 2006;4:58.
67. Cremeens J, Eiser C, Blades M. Characteristics of health-related self-reported measure for children aged three to eight years: a review of the literature. *Quality of Life Research.* 2006;15(4):739-754.
68. Brown JS. Growing up digital: how the web changes work, education, and the ways people learn. *Change.* 2000;32(2):11-20.
69. Oblinger D, Oblinger JL, Lippincott JK. *Educating the Net Generation.* Boulder, CO: EDUCAUSE; 2005.
70. Bates AW, Poole G. *Effective Teaching with Technology in Higher Education: Foundations for Success.* Indianapolis, IN: Jossey-Bass, An Imprint of Wiley; 2003.
71. Lenhart A, Kahne J, Middaugh E, Macgill A, Evans C, Vitak J; Pew Research Center. Teens, Video Games and Civics. Published September 16 2008.
72. Lee JJ, Hammer J. Gamification in education: what, how, why bother? *Academic Exchange Quarterly.* 2011;15(2):146.
73. King D, Greaves F, Exeter C, Darzi A. "Gamification": influencing health behaviours with games. *Journal of the Royal Society of Medicine.* 2013;106(3):76-78.
74. McCallum S. Gamification and serious games for personalized health. *Stud Health Technol Inform.* 2012;177:85-96.
75. Stinson JN, Jibb LA, Nguyen C, et al. Development and testing of a multidimensional iPhone pain assessment application for adolescents with cancer. *Journal of Medical Internet Research.* 2013;15(3):e51. doi: 10.2196/jmir.2350.Pmc3636147
76. Jibb LA, Stevens BJ, Nathan PC, Seto E, Cafazzo JA, Stinson JN. A smartphone-based pain management app for adolescents with cancer: establishing system requirements and a pain care algorithm based on literature review, interviews, and consensus. *JMIR Research Protocols.* 2014;3(1):e15.Pmc3978558

77. Fortier MA, Chung WW, Martinez A, Gago-Masague S, Sender L. Pain buddy: a novel use of m-health in the management of children's cancer pain. *Computers in Biology and Medicine.* 2016;76:202-214. doi: 10.1016/j.compbiomed.2016.07.012.PMC5639256
78. Gary KA, Rallabhandi P, Walek E, et al. An mHealth hybrid app for self-reporting pain measures for sickle cell disease. 2016 IEEE Healthcare Innovation Point-Of-Care Technologies Conference (HI-POCT); 9-11 Nov; Cancun, Mexico.
79. Stinson JN, Jibb LA, Nguyen C, et al. Construct validity and reliability of a real-time multidimensional smartphone app to assess pain in children and adolescents with cancer. *Pain.* 2015;156(12):2607-2615. doi: 10.1097/j.pain.0000000000000385
80. Jonassaint CR, Shah N, Jonassaint J, De Castro L. Usability and feasibility of an mHealth intervention for monitoring and managing pain symptoms in sickle cell disease: the Sickle Cell Disease Mobile Application to Record Symptoms via Technology (SMART). *Hemoglobin.* 2015;39(3):162-168.
81. Jibb LA, Stevens BJ, Nathan PC, et al. Implementation and preliminary effectiveness of a real-time pain management smartphone app for adolescents with cancer: A multicenter pilot clinical study. *Pediatr Blood and Cancer.* 2017;64(10) doi: 10.1002/pbc.26554
82. Lieberman DA. Management of chronic pediatric diseases with interactive health games: theory and research findings. *Journal of Ambulatory Care Management.* 2001;24(1):26-38.
83. Abras C, Maloney-Krichmar D, Preece J. User-centered design. In: Bainbridge, W, ed. *Encyclopedia of Human-Computer Interaction.* Vol 37. Thousand Oaks: Sage Publications; 2004:445-456.
84. Norman DA, Draper SW. *User Centered System Design: New Perspectives on Human-Computer Interaction.* Hillsdale, NJ: Lawrence Erlbaum Associates Inc.; 1986.
85. Deci EL. Effects of externally mediated rewards on intrinsic motivation. *Journal of Personality and Social Psychology.* 1971;18:105-115.
86. Deci EL, Ryan RM. *Handbook of Self-Determination Research.* University Rochester Press; 2004.
87. Bandura A. *Social Foundations of Thought and Action: A Social Cognitive Theory.* Englewood Cliffs NJ: Prentice Hall; 1986.
88. Mazzara ML; IBM. Application of theory: minimalism and user centered design. Available at: http://www.gotomedia.com/goto/web2expo/workshop/resources/minimialism_ucd.pdf. 2001. Accessed December 20, 2017.
89. Pagulayan RJ, Keeker K, Wixon D, Romero RL, Fuller T. User-centered design in games. In: Sears, A, Jacko, JA, eds. *Human-Computer Interaction Handbook: Fundamentals, Evolving Technologies and Emerging Applications*. Mahwah, NJ: Lawrence Erlbaum Associaties, Inc.; 2003:883-906.
90. Silva MN, Markland D, Minderico CuS, et al. A randomized controlled trial to evaluate self-determination theory for exercise adherence and weight control: rationale and intervention description. *BMC Public Health.* 2008;8(1):234.
91. Silva MN, Vieira PN, Coutinho SlR, et al. Using self-determination theory to promote physical activity and weight control: a randomized controlled trial in women. *J Behav Med.* 2010;33(2):110-122.
92. Ryan RM, Patrick H, Deci EL, Williams GC. Facilitating health behaviour change and its maintenance: interventions based on Self-Determination Theory. *The European Health Psychologist.* 2008;10(1):2-5.
93. Vansteenkiste M, Soenens B, Vandereycken W. Motivation to change in eating disorder patients: a conceptual clarification on the basis of self-determination theory. *International Journal of Eating Disorders.* 2005;37(3):207-219.
94. Markland D, Ryan RM, Tobin VJ, Rollnick S. Motivational interviewing and self-determination theory. *Journal of Social and Clinical Psychology.* 2005;24(6):811-831.
95. Rogers ER, King SR. Intervention based on social cognitive theory: evaluating adolescents' knowledge of OTC pain medications. *Journal of the American Pharmaceutical Association (American Pharmaceutical Association).* 2013;53(1):30-38. doi: 10.1331/JAPhA.2013.11231

96. Edwards LY, Edwards CL. Psychosocial treatments in pain management of sickle cell disease. *Journal of the National Medical Association.* 2010;102:1084-1094.
97. Lewis Hobart M. Learning from myself: avatars and educational video games. *Current Issues in Education.* 2012;15(3)
98. Gazzard A. The avatar and the player: understanding the relationship beyond the screen. 2009. Accessed 2013/03/23/.
99. Kaufman GF, Libby LK. Changing beliefs and behavior through experience-taking. *Journal of Personality and Social Psychology.* 2012;103(1):1.
100. Hope & Destiny Jr. - The Adolescents Guide to Sickle Cell Diseases book information. Hilton Publishing Company Website. Available at: http://www.hiltonpub.com/bookstore/products/205314-hope-destiny-jr-the-adolescents-guide-to-sickle-cell-diseases.aspx. Accessed April 5, 2015.
101. Zempsky WT. Evaluation and treatment of sickle cell pain in the emergency department: paths to a better future. *Clinical Pediatric Emergency Medicine.* 2010;11(4):265-273.Pmc3076949
102. Pack-Mabien A, Labbe E, Herbert D, Haynes J, Jr. Nurses' attitudes and practices in sickle cell pain management. *Applied Nursing Research.* 2001;14(4):187-192.
103. Labbe E, Herbert D, Haynes J. Physicians' attitude and practices in sickle cell disease pain management. *Journal of Palliative Care.* 2005;21(4):246-251.
104. Shapiro BS, Benjamin LJ, Payne R, Heidrich G. Sickle cell-related pain: perceptions of medical practitioners. *Journal of Pain and Symptom Management.* 1997;14(3):168-174.
105. Greenhalgh J, Meadows K. The effectiveness of the use of patient-based measures of health in routine practice in improving the process and outcomes of patient care: a literature review. *Journal of Evaluation in Clinical Practice.* 1999;5(4):401-416.
106. Varni JW, Burwinkle TM, Lane MM. Health-related quality of life measurement in pediatric clinical practice: an appraisal and precept for future research and application. *Health and Quality of Life Outcomes.* 2005;3(1):34.
107. Sickle cell disease: national resource directory. Centers for Disease Control and Prevention Web site. Available at: https://www.cdc.gov/ncbddd/sicklecell/map/map-nationalresourcedirectory.html. Published 2011. Updated June 19, 2017. Accessed December 28, 2017.
108. Brooke J. SUS-A quick and dirty usability scale. In: Jordan, PW, Thomas, B, Weerdmeester, BA, McClelland, IL, eds. *Usability evaluation in industry*. London: Taylor & Francis; 1996:189-194.
109. Krueger RA, Casey MA. *Focus Groups: A Practical Guide for Applied Research.* Sage; 2009.
110. Jones FC, Broome ME. Focus groups with African American adolescents: enhancing recruitment and retention in intervention studies. *Journal of Pediatric Nursing.* 2001;16(2):88-96.
111. UserTesting. What is remote usability testing? *User Testing Blog.* Vol 2017: User Testing Web site. Available at: https://www.usertesting.com/blog/2015/11/30/what-is-remote-usability-testing/.
112. UserTesting. The UX Research Methodology guidebook. UserTesting Web site. Available at: https://info.usertesting.com/UX-Research-Methodology-Guidebook.html?utm_source=blog&utm_campaign=ps. Accessed December 29, 2017.
113. Kanneganti S. 5 reason for going remote with mobile website usability testing. *UserZoom Blog.* Vol 2017. Available at: https://www.userzoom.com/mobile-usability-testing/5-reasons-for-going-remote-with-mobile-website-usability-testing/.
114. Remote testing. usability.gov Web site. Available at: https://www.usability.gov/how-to-and-tools/methods/remote-testing.html. Accessed December 29, 2017.
115. Martin R, Al Shamari M, Seliaman M, Mayhew PJ. Remote asynchronous testing: a cost-effective alternative for website usability evaluation. *International Journal of Computer and Information Technology.* 2014;3(1):99-104.
116. Bangor A, Kortum P, Miller J. Determining what individual SUS scores mean: Adding an adjective rating scale. *J Usability Stud.* 2009;4(3):114-123.

117. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. *Int J Hum Comput Interact.* 2008;24(6):574-594.
118. Peterson C. Bringing ADDIE to life: instructional design at its best. *Journal of Educational Multimedia and Hypermedia.* 2003;12(3):227-241.
119. Gustafson KL, Branch RM. What is instructional design? In: Reiser, RA, Dempsey, JV, eds. *Trends and Issues in Instructional Design and Technology*. Columbus, OH: Merril/Prentice Hall; 2002.
120. Molenda M. In search of the elusive ADDIE model. *Performance Improvement.* 2015;54(2):40-42.
121. Hunicke R, LeBlanc M, Zubek R. MDA: a formal approach to game design and game research. 2004.
122. Zichermann G, Cunningham C. *Gamification by Design: Implementing Game Mechanics in Web and Mobile Apps.* O'Reilly Media, Inc.; 2011.
123. Dattatreya V, Chalapati Rao KV. Agile programming and design patterns in web development - a case study. *International Journal of Software Engineering & Applications.* 2012;3(1):37-45.
124. Khalid A, Zahra S, Khan MF. Suitability and contribution of agile methods in mobile software development. *International Journal of Modern Education and Comupter Science.* 2014;2:56-62.
125. Hope for SCD, Rose L. *Sickle What?* 1 ed. Munster, IN: Hilton Publishing; 2016.
126. Cafazzo JA, Casselman M, Hamming N, Katzman DK, Palmert MR. Design of an mHealth app for the self-management of adolescent type 1 diabetes: a pilot study. *Journal of medical Internet research.* 2012;14(3):e70.
127. Graafland M, Dankbaar M, Mert A, et al. How to systematically assess serious games applied to health care. *JMIR serious games.* 2014;2(2)
128. Kulyk O, den Daas C, David S, van Gemert-Pijnen L. How Persuasive are Serious Games, Social Media and mHealth Technologies for Vulnerable Young Adults?
129. Hieftje K, Duncan L, Sawyer B, Haskell S, Fiellin L. A Tablet Game for Risk Reduction and HIV Prevention in Adolescents. *Journal of Mobile Technology in Medicine.* 2012;1(4S):8-8.
130. Shegog R, Brown K, Bull S, et al. Serious games for sexual health. *Games for Health Journal.* 2015;4(2):69-77.
131. Nah FFH, Telaprolu VR, Rallapalli S, Venkata PR. Gamification of education using computer games. *Human Interface and the Management of Information. Information and Interaction for Learning, Culture, Collaboration and Business*: Springer; 2013:99-107.
132. Initiative EL. 7 things you should know about BADGES. 2012. https://net.educause.edu/ir/library/pdf/ELI7085.pdf.
133. Easley D, Ghosh A. Incentives, gamification, and game theory: an economic approach to badge design. Paper presented at: Proceedings of the fourteenth ACM conference on Electronic commerce2013.
134. Miller AS, Cafazzo JA, Seto E. A game plan: Gamification design principles in mHealth applications for chronic disease management. *Health informatics journal.* 2014:1460458214537511.
135. Faulkner L. Beyond the five-user assumption: benefits of increased sample sizes in usability testing. *Behavior Research Methods, Instruments, & Computers.* 2003;35(3)
136. Macefield R. How to specify the participant group size for usability studies: a practitioner's guide. *Journal of Usability Studies.* 2009;5(1)
137. Turner CW, Lewis JR, Nielsen J. Determining usability test sample size. In: Karwowski, W, ed. *International Encyclopedia of Ergonomics and Human Factors.* Vol 2nd. Boca Raton, FL: CRC Press; 2006:3084-3088.
138. Sauro J, Lewis JR. *Quantifying the User Experience: Practical Statistics for User Research.* Morgan Kaufmann; 2012.
139. Sauro J. *A Practical Guide to Measuring Usability: 72 Answers to the Most Common Questions About Quantifying the Usability of Websites and Software.* CreateSpace Independent Publishing Platform; 2010.

140. Sim G, MacFarlane S, Read J. All work and no play: measuring fun, usability, and learning in software for children. *Computers & Education.* 2006;46:235-248.

141. Brooke J. SUS - A quick and dirty usability scale. In: Jordan, PW, Thomas, B, Weerdmeester, BA, McClelland, IL, eds. *Usability Evaluation in Industry*. London: Taylor & Francis; 1996:189-194.

142. Bangor A, Kortum P, Miller J. Determining what individual SUS scores mean: adding an adjective rating scale. *Journal of Usability Studies.* 2009;4(3):114-123.

143. Bangor A, Kortum PT, Miller JT. An empirical evaluation of the system usability scale. *International Journal of Human-Computer Interaction.* 2008;24(6):574-594.

144. Shadish WR, Cook TD, Campbell DT. *Experimental and Quasi-Experimental Designs for Generalized Causal Inference.* Boston, MA: Houghton Mifflin Company; 2002.

145. Germain ML. Stages of psychometric measure development: the example of the generalized expertise measure (GEM). 2006

146. Lawshe CH. A quantitative approach to content validity1. *Pers Psychol.* 1975;28(4):563-575.

147. Hinkin TR. A review of scale development practices in the study of organizations. *J Manage.* 1995;21(5):967-988.

148. Nunnally JC. *Psychometric Theory.* New York, NY: McGraw-Hill; 1978.

149. Varni JW, Magnus B, Stucky BD, et al. Psychometric properties of the PROMIS (R) pediatric scales: precision, stability, and comparison of different scoring and administration options. *Quality of Life Research.* 2014;23(4):1233-1243. doi: 10.1007/s11136-013-0544-0.PMC4312615

150. DeWalt DA, Gross HE, Gipson DS, et al. PROMIS(R) pediatric self-report scales distinguish subgroups of children within and across six common pediatric chronic health conditions. *Quality of Life Research.* 2015;24(9):2195-2208. doi: 10.1007/s11136-015-0953-3.PMC4531096

151. Treadwell M, Johnson S, Sisler I, et al. Development of a sickle cell disease readiness for transition assessment. *International Journal of Adolescent Medicine and Health.* 2016;28(2):193-201. doi: 10.1515/ijamh-2015-0010

152. Johnson A, Waters P, Griffin A, et al. Stepping Up To Adult Care: Developing a Healthcare Transition Program For Pediatric Sickle Cell Disease Populations.

153. Newland JA. Factors influencing independence in adolescents with sickle cell disease. *Journal of Child and Adolescent Psychiatric Nursing.* 2008;21(3):177-185. doi: 10.1111/j.1744-6171.2008.00149.x

154. Barakat LP, Schwartz LA, Salamon KS, Radcliffe J. A family-based randomized controlled trial of pain intervention for adolescents with sickle cell disease. *Journal of Pediatric Hhematology/Oncology.* 2010;32(7):540-547. doi: 10.1097/MPH.0b013e3181e793f9

155. Clay OJ, Telfair J. Evaluation of a disease-specific self-efficacy instrument in adolescents with sickle cell disease and its relationship to adjustment. *Child Neuropsychology.* 2007;13(2):188-203. doi: 10.1080/09297040600770746

156. Landgraf JM, Abetz L, Ware JE. *The CHQ User's Manual.* Boston: The Health Institute, New England Medical Center; 1996.

157. Raat H, Botterweck AM, Landgraf JM, Hoogeveen WC, Essink-Bot M-L. Reliability and validity of the short form of the child health questionnaire for parents (CHQ-PF28) in large random school based and general population samples. *Journal of Epidemiology and Community Health.* 2005;59(1):75.

158. Robinson KA, Dennison CR, Wayman DM, Pronovost PJ, Needham DM. Systematic review identifies number of strategies important for retaining study participants. *Journal of Clinical Epidemiology.* 2007;60(8):757-765. doi: 10.1016/j.jclinepi.2006.11.023.PMC1997303

159. Coday M, Boutin-Foster C, Goldman Sher T, et al. Strategies for retaining study participants in behavioral intervention trials: retention experiences of the NIH Behavior Change Consortium. *Annals of Behavioral Medicine.* 2005;29 Suppl:55-65. doi: 10.1207/s15324796abm2902s_9

160. Nicholson LM, Schwirian PM, Groner JA. Recruitment and retention strategies in clinical studies with low-income and minority populations: Progress from 2004-2014. *Contemporary Clinical Trials.* 2015;45(Pt A):34-40. doi: 10.1016/j.cct.2015.07.008
161. Karlson CW, Rapoff MA. Attrition in randomized controlled trials for pediatric chronic conditions. *Journal of Pediatric Psychology.* 2009;34(7):782-793. doi: 10.1093/jpepsy/jsn122
162. Krueger RA. *Focus groups: A practical guide for applied research.* Sage; 2009.
163. Tucker JA, Roth DL, Huang J, Crawford MS, Simpson CA. Effects of interactive voice response self-monitoring on natural resolution of drinking problems: utilization and behavioral economic factors. *Journal of Studies on Alcohol and Drugs.* 2012;73(4):686.
164. Fritz MS, MacKinnon DP. Required sample size to detect the mediated effect. *Psychological Science.* 2007;18(3):233-239.
165. MacKinnon DP, Lockwood CM, Williams J. Confidence limits for the indirect effect: distribution of the product and resampling methods. *Multivariate Behavioral Research.* 2004;39(1):99.

Statistical Analysis Plan

Statistical Power Calculations and Analysis.

Sample size: The primary outcome is detecting a positive change on the knowledge acquisition questionnaire (communication skill and pain identification). To be conservative, we assumed that 80% of those offered the app will have baseline and post-test results. Our sample size of 100 allows for up to 20% dropouts. We expect results similar to those found by Barakat et.al.[159] on our secondary outcome measures (which were similar to ours). We used their results to derive our nonparametric sample sizes on SCD disease-specific and transition knowledge, and family cohesion. For the transition knowledge construct, assuming the correlation before-to-after is 0.5, the sample size is N=22, using power of 80% and a Bonferroni corrected Type I error of 0.0167. For disease-specific knowledge, the sample size necessary to achieve 80% power is 76 participants, using the same assumptions (Type I error of 0.0167). For the third outcome (i.e., family cohesion), if we assume 80 participants at all time points, then the power is somewhat lower since the sample size required to achieve 80% power is 132 (mean difference between post-test and baseline was 6.51 with a pooled standard deviation of 22.8). For this outcome, the power with 80 participants is 54%. We weighed the importance of the first two outcomes (disease-specific and transition knowledge) relative to the increase in cost and duration to increase the sample to 165 (i.e., 132 plus dropouts up to 20%) to account for the single-item family cohesion variable. We felt that having greater than 50% power for family cohesion and sufficient power for the participant-related measures (80% for SCD disease-specific and transition knowledge), we would not increase the sample size by 65% (i.e., from 100 to 165) in order to achieve 80% power for family cohesion. We have nevertheless left it in, because we respect its importance. As a Phase II study, we believe that we can accept less power on that single measure given consistency of outcomes will drive further evolution of this product.

Analyses: There are 2 aims that will be evaluated (AIMs 2 and 3). As a Phase II SBIR, the analyses are heavily descriptive in nature for this trial. Means (standard deviations), medians (interquartile range), distributions, frequencies and percentiles, etc. will be used to characterize the outcome measures.

For Aim 2 (Usability), 14 users are needed to identify any problems that impact $\geq$15% of users at a 90% chance of detection (log(1-.90)/log(1-.15)). Data on applied formative research suggests that 5 participants is sufficient to identify likes/dislikes and potential errors; thus, the power to detect Level 1 severity usability errors should be more than sufficient with n=14.[167] Similar to Phase I, usability outcomes will also include program satisfaction ratings with regards to design, appeal, and functionality. Each concept will be rated on a 5-point Likert scale. Means will be calculated and an average of 67% or higher will be considered acceptable. We will examine mean scores, changes in mean scores, and variation within geographical location. The SUS will serve as the primary criterion for measuring usability.[113,121,122] Further, we will look for outliers to assess if there may be specific characteristics of users who have or develop problems as the processes evolve.

Effectiveness (AIM 3) is critical to product development and will evaluate whether *Pinpoint* increases communication and pain identification knowledge. Means (standard deviations), medians (interquartile range), distributions, frequencies and percentiles will be used to characterize the primary outcome measure. We will test the within person change over time for knowledge acquisition, SCD disease-specific and transition knowledge, SCD self-efficacy, and family cohesion. Linear regression will assess the effects of age, **biologic sex**, and education. Parents will complete a proxy version of the primary outcome; child and parent-report agreement will be assessed using intra-class correlations and median difference tested using Wilcoxon significance tests. Kolmogorov-Smirnov tests will assess for normal score distribution.

Characteristics of dropouts and/or noncompliant individuals will be examined to shed light on potential weaknesses of the app (differential dropout overall or within certain subgroups). Utilization data will be examined to understand the acceptability and intensity of interactions with the app. The penetration of the app into this at-risk population is very important in understanding potential impact. Complier average causal effect models[168] will be used to examine the intensity of the app's utilization. Mediation models using the latest bootstrapping methods[169,170] will be examined to provide evidence that the changes induced by the treatment effects are consistent with the changes being mediated via the app.

As a sensitivity analysis to demonstrate discordant validity, we will perform the same analysis as on the primary outcome, using the number of correct answers in the CDC Flu IQ (i.e., nonequivalent dependent variable). This outcome should not be impacted by the intervention and we expect to see no change in the mean number correct. Although failure to show a difference is not evidence for no difference, the discordant effect size should provide additional information that the primary results are consistent with an intervention effect.

Evidence for Scientific Rigor and Potential Limitations. The study has numerous strengths, few limitations, and is scientifically rigorous. The study is theory-driven (i.e., User-centered Design and Social Cognitive theories). Formative data will incorporate multiple stakeholder input. The programming approach will be multi-model and evidence-based (i.e., ADDIE Model, MDA framework, AGILE programming) resulting in a systematic, flexible, and cost-effective approach. Sample sizes are sufficient and supported by the literature. Effectiveness will be evaluated in a within-subjects design which allows for sufficient power (i.e., statistical inference with fewer subjects), efficiency (i.e., quicker trial completion), and longitudinal analysis (i.e., individual changes over time). The study team and environment are strong. Potential limitations are: (1) difficulty recruiting; (2) sources of bias; and (3) lack of control group. We have tried to reduce their impact. We will work closely with the EAB and PAB to maximize recruitment. Our primary outcome measure is new, but we are using a rigorous approach to scale development. Self-report instruments are open to bias, however the use of validated measures is a strength. Limitations of no control group are lessened via the use of a time-series design for outcome changes and testing of a nonequivalent dependent variable.